

## **A Phase 2a Randomized, Blinded, Placebo-controlled Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of MEDI6012 in Subjects with Stable Atherosclerotic Cardiovascular Disease**

**Sponsor Protocol Number:** D5780C00005

**Application Number:** IND number 113,358

**Investigational Product:** MEDI6012 (recombinant human lecithin-cholesterol acyltransferase)

**Sponsor:** MedImmune, LLC, a wholly owned subsidiary of AstraZeneca PLC, One MedImmune Way, Gaithersburg, Maryland, 20878, USA

**Medical Monitor:** [REDACTED]  
Medical Director, Clinical Development, MedImmune

**Study Chair:** [REDACTED]  
Chairman, TIMI Study Group  
[REDACTED] Distinguished Chair in Cardiovascular Medicine  
Brigham and Women's Hospital  
Professor of Medicine, Harvard Medical School

**Principal Investigator:** [REDACTED]  
Investigator, TIMI Study Group  
Associate Physician, Brigham and Women's Hospital  
Instructor, Harvard Medical School

**Contract Research Organization:** Medpace

**Protocol History, Date:** Original Protocol, 23Nov2016  
Amendment 1, 16Jul2017

## PROTOCOL SYNOPSIS

<p><b>TITLE</b></p> <p>A Phase 2a Randomized, Blinded, Placebo-controlled Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Ascending Doses of MEDI6012 in Subjects with Stable Atherosclerotic Cardiovascular Disease</p>
<p><b>HYPOTHESES</b></p> <p><b>Primary Hypotheses:</b></p> <ol style="list-style-type: none"><li>1. Repeat dosing with MEDI6012 exhibits an acceptable safety profile in subjects with stable atherosclerotic cardiovascular disease (CVD).</li><li>2. Repeat dosing with MEDI6012 results in a sustained and reversible dose-dependent response for high-density lipoprotein-cholesterol (HDL-C), cholesteryl ester (CE), and high-density lipoprotein-cholesteryl ester (HDL-CE) that allows once weekly or less frequent dosing.</li></ol> <p><b>Secondary Hypotheses:</b></p> <ol style="list-style-type: none"><li>1. Repeat dosing with MEDI6012 will result in a pharmacokinetic (PK) profile (lecithin-cholesterol acyltransferase [LCAT] mass and LCAT activity) that allows once weekly or more frequent dosing.</li><li>2. A regimen comprised of an initial loading dose of MEDI6012 followed by a dose at 48 hours and 1 week later will result in a rapid rise in HDL-C and apolipoprotein A1 (apoA1) compared with no loading dose and maintenance of pharmacodynamic (PD) effect for 7 or more days.</li><li>3. Repeat dosing with MEDI6012 results in dose-dependent responses for other key PD biomarkers in subjects with stable atherosclerotic CVD.</li><li>4. Repeat dosing with MEDI6012 does not result in the development of neutralizing anti-drug antibodies (nAb) that cross-react with endogenous LCAT leading to decreased HDL-C.</li></ol>
<p><b>OBJECTIVES</b></p> <p><b>Primary Objectives:</b></p> <ol style="list-style-type: none"><li>1. The primary safety objective is to evaluate the safety of MEDI6012 following repeat dosing in subjects with stable atherosclerotic CVD over time to Day 71 (Cohorts 1-3) or Day 66 (Cohort 4).</li><li>2. The primary PD objective is to establish that repeat dosing with MEDI6012 results in a sustainable and reversible dose-dependent response for HDL-C, HDL-CE, and CE.</li></ol> <p><b>Secondary Objectives:</b></p> <ol style="list-style-type: none"><li>1. To establish the PK profile of MEDI6012 following repeat-dose administration.</li><li>2. To establish the PD effect of MEDI6012 following an initial loading dose followed by a dose at 48 hours and 1 week later (Cohort 4 only).</li><li>3. To evaluate the effect of MEDI6012 on a range of PD biomarkers following repeat dose administration.</li><li>4. To evaluate the immunogenicity potential of MEDI6012.</li></ol> <p><b>Exploratory Objective:</b></p> <ol style="list-style-type: none"><li>1. [REDACTED]</li></ol>
<p><b>STUDY ENDPOINTS</b></p> <p><b>Primary Safety Endpoint</b></p> <p>Safety and tolerability of MEDI6012 as measured by the incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs) and clinically important changes in 12-lead electrocardiogram, vital signs, and clinical laboratory evaluations over time to Day 71 (Cohorts 1-3) Day 66 (Cohort 4).</p> <p><b>Primary PD Endpoint:</b></p> <p>Baseline adjusted area under the concentration-time curve from time 0 to 96 hours post dose 3(AUC<sub>0-96hr</sub>) for HDL-C, HDL-CE, and CE.</p> <p><b>Secondary Endpoints:</b></p> <ol style="list-style-type: none"><li>1. PK for MEDI6012 mass and activity</li></ol>

2. Serum concentration of other key lipids and lipoproteins: CE, HDL-CE, HDL-unesterified cholesterol, (HDL-UC), non-HDL-C, non-HDL-CE, non-HDL-UC, low density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apoB), triglycerides (TG), very low-density lipoprotein-cholesterol (VLDL-C), free cholesterol (FC), and apoA1, apoAII, apoCIII, apolipoprotein E (apoE), pre $\beta$ 1-HDL
  3. Anti-drug antibodies (ADA) and nAb development, with concomitant decreases in HDL-C.
- Exploratory Endpoint:**
1. [REDACTED]

**STUDY DESIGN**

This is a Phase 2a randomized, blinded (subject/investigator blinded, MedImmune unblinded), placebo-controlled, dose-escalation study to evaluate the safety, PK/PD, and immunogenicity of repeat doses of MEDI6012 in adult subjects with stable atherosclerotic CVD. At least 32 subjects are planned to be randomized across approximately 10 study sites in the United States of America (USA) to evaluate 4 dose levels (40, 120, 300 mg, and an IV push dosing regimen that includes a loading dose of 300 mg followed by a 150 mg maintenance dose at 48 hours and a 100 mg maintenance dose 7 days later) of MEDI6012. Subjects in Cohorts 1-3 will be administered investigational product weekly via intravenous (IV) infusions. Cohort 4 subjects will be administered investigational product using a loading dose of 300 mg (Dose 1) of MEDI6012, a second dose of 150 mg at 48 hours followed by a maintenance dose of 100 mg 1 week later with all doses given by IV push. For each cohort, 8 subjects are planned for randomization in a 6:2 ratio to receive MEDI6012 or placebo. Investigational product will be administered as a 1-hour IV infusion (Cohorts 1-3) or an IV push (Cohort 4).

Subjects will undergo a screening period of up to 28 days. For subjects requiring a washout of dyslipidemia medication or supplement, a 56 day screening period is allowed. Subjects will be admitted to the study center the evening prior to randomization and first dose administration (Day -1) and prior to third dose administration and remain at the study center for 24-36 hours. In lieu of overnight admission, outpatient arrangements such as a hotel stay near the study center or return to home may alternatively be provided. For dose 2, subjects will be observed as inpatients for at least 8 hours following dosing. For Cohort 4, outpatient arrangements may be provided through Day 4. Subjects will be followed as outpatients through 56 days after the last dose of investigational product (Day 71 visit for Cohorts 1-3, Day 66 visit for Cohort 4). Subjects will be encouraged to maintain a healthy lifestyle, including diet and exercise, during the study period.

If a subject's Day 71 (Cohorts 1-3) or Day 66 (Cohort 4) immunogenicity sample is confirmed as ADA positive, the subject will return to the study site on Weeks 14 and 18 and approximately every 3 months thereafter (or more frequently) for additional assessments until their immunogenicity sample is no longer ADA positive or until approximately 12 months after the Day 43 (Cohorts 1-3) or Day 38 (Cohort 4) visit, whichever occurs first. If a MedImmune safety review board determines that an adverse safety signal is attributed to the ADA-positive signal, then follow up may continue beyond 12 months for subjects whose immunogenicity sample continues to be ADA positive.

**TARGET SUBJECT POPULATION**

Adult men or women, aged 60 through 80 years with a history of documented stable atherosclerotic CVD.

**INVESTIGATIONAL PRODUCT, DOSAGE, AND MODE OF ADMINISTRATION**

- Cohort 1: 40 mg MEDI6012 (n = 6) or placebo (n = 2) IV on Days 1, 8, and 15
- Cohort 2: 120 mg MEDI6012 (n = 6) or placebo (n = 2) IV on Days 1, 8, and 15
- Cohort 3: 300 mg MEDI6012 (n = 6) or placebo (n = 2) IV on Days 1, 8, and 15
- Cohort 4: 300 mg of MEDI6012 on Day 1 (loading dose), a second dose of 150 mg at 48 hours (maintenance dose on Day 3) followed by 100 mg 1 week later (maintenance dose on Day 10) by IV push.

## STATISTICAL ANALYSIS PLAN

### Sample Size:



### Statistical Analyses:

Safety analysis will be based on the As-treated Population. Adverse event (AE) and serious adverse event collection begins after the subject signs the informed consent document and lasts until the end of study visit. TEAEs and TESAEs will be coded by the most updated version of the Medical Dictionary for Regulatory Activities (MedDRA), and the type incidence, severity, and relationship to investigational product will be summarized. Specific AEs will be counted once for each subject for calculating percentages. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of relationship observed will be reported. All TEAEs and TESAEs will be summarized overall, as well as categorized by MedDRA system organ class and preferred term.

The PD parameters of primary interest are the baseline adjusted AUC from time 0 to 96 hours post dose 3 in HDL-C ( $AUC_{0-96hr \text{ Dose } 3}$ ), HDL-CE, and CE. AUC will be calculated using the trapezoidal rule. Statistical comparison between treatment groups with placebo group combined will be conducted using analysis of covariance (ANCOVA) by adjusting baseline HDL-C, HDL-CE, and CE and treatment group. Other endpoints including  $AUC_{0-96hr \text{ Dose } 1}$ ,  $AUC_{0-168hr \text{ Dose } 1}$ ,  $AUC_{0-168hr \text{ Dose } 3}$  (AUC from time 0 on Day 1 through 168 hours after Dose 3),  $AUC_{1-22d}$ , HDL-C, TC, FC, CE, HDL-CE, HDL-UC, non-HDL-C, non-HDL-CE, non-HDL-UC, LDL C (by direct measure), apoA1, and apoB, will be analyzed similarly to the primary PD endpoint.

Change and the percent change from baseline at each time point for each of the above lipids, lipoproteins, and apolipoproteins as well as VLDL-C, TG, pre $\beta$ 1-HDL, apoA1, apoAII, apoCIII, and apoE will be analyzed and compared using ANCOVA by adjusting baseline and treatment group with placebo group combined.

For ANCOVA, if the data is not normally distributed, the analyses will be conducted on rank-transformed data.

Descriptive statistics will be provided by treatment group for maximum biomarker response ( $R_{max}$ ) and time to reach maximum biomarker response ( $[R] T_{max}$ ) for each of these as well.

ADA incidence rate and titer will be tabulated for each treatment group. Samples confirmed positive for ADA will be tested and analyzed for nAb and summarized similarly.

Non-compartmental analysis will be performed for MEDI6012 treated subjects. Serum MEDI6012 mass and activity concentration-time profiles will be summarized by dose cohort. The PK parameters to be reported include maximum plasma concentration of the drug ( $C_{max}$ ), time of maximal concentration ( $T_{max}$ ), AUC, accumulation ratio and terminal half-life ( $t_{1/2}$ ). Descriptive statistics for PK parameters will be provided.

Additional PK analyses may be conducted as appropriate. If the data allow, population PK analysis will be performed but will not be reported within the clinical study report (CSR).

**Primary analysis:** A primary analysis of the safety, immunogenicity, PK, and PD data will be conducted after the last subject has completed or dropped out prior to the last scheduled visit (Day 71 for Cohorts 1-3 or Day 66 for Cohort 4) and will be reported in the CSR. The long-term follow-up data for ADA positive subjects will be reported as an addendum to the CSR.

## TABLE OF CONTENTS

PROTOCOL SYNOPSIS .....	2
LIST OF ABBREVIATIONS.....	10
1 INTRODUCTION.....	12
1.1 Disease Background .....	12
1.2 MEDI6012 Background.....	13
1.3 Summary of Nonclinical Experience.....	14
1.4 Summary of Clinical Experience.....	14
1.5 Rationale for Conducting the Study .....	15
1.6 Research Hypotheses .....	16
1.6.1Primary Hypotheses.....	16
1.6.2Secondary Hypotheses.....	16
2 OBJECTIVES .....	17
2.1 Objectives .....	17
2.1.1Primary Objective.....	17
2.1.2Secondary Objectives .....	17
2.1.3Exploratory Objective.....	17
2.2 Study Endpoints.....	18
2.2.1Primary Endpoint.....	18
2.2.2Secondary Endpoints .....	18
2.2.3Exploratory Endpoint.....	18
3 STUDY DESIGN.....	18
3.1 Description of the Study .....	18
3.1.1Overview.....	18
3.1.2Treatment Regimen.....	20
3.1.3Dose Escalation.....	21
3.2 Study Design and Dose Rationale .....	23
3.2.1Dose Rationale for Cohorts 1-3 .....	23
3.2.2Dose Rationale for Cohort 4.....	28
3.2.3Rationale for Study Population.....	33
3.2.4Rationale for Endpoints .....	33
3.2.4.1 Rationale for Primary Endpoint.....	33
3.2.4.2 Rationale for Other Key PD Endpoints .....	34
3.2.4.3 Rationale for PK Endpoints .....	34
3.2.4.4 Rationale for Immunogenicity Endpoints.....	34
3.2.4.5 Rationale for Exploratory PD Endpoints .....	34
4 MATERIALS AND METHODS.....	35
4.1 Subjects.....	35

4.1.1	Number of Subjects .....	35
4.1.2	Inclusion Criteria .....	35
4.1.3	Exclusion Criteria .....	36
4.1.4	Subject Enrollment and Randomization .....	38
4.1.5	Withdrawal from the Study.....	39
4.1.6	Discontinuation of Investigational Product .....	39
4.1.7	Replacement of Subjects.....	40
4.1.8	Withdrawal of Informed Consent for Data and Biological Samples .....	40
4.2	Schedule of Study Procedures .....	41
4.2.1	Unscheduled Visits and Early Termination Visits.....	50
4.3	Description of Study Procedures .....	51
4.3.1	Medical History, Physical Examination, Electrocardiograms, Weight, and Vital Signs .....	51
4.3.1.1	Medical History and Physical Examination.....	51
4.3.1.2	Systemic/Local Tolerability.....	52
4.3.1.3	Vital Signs.....	52
4.3.1.4	Electrocardiograms .....	53
4.3.2	Clinical Laboratory Tests.....	54
4.3.3	Pharmacokinetic Evaluation and Methods .....	55
4.3.4	Pharmacodynamic Evaluation and Methods.....	56
4.3.5	Immunogenicity Evaluation and Methods .....	56
4.3.6	Estimate of Blood Volume to Be Collected.....	57
4.4	Study Suspension or Termination.....	58
4.5	Investigational Products.....	59
4.5.1	Identity of Investigational Product .....	59
4.5.1.1	Investigational Product Dose Handling .....	60
4.5.1.2	Investigational Product Inspection.....	62
4.5.1.3	Dose Preparation Steps .....	62
4.5.1.4	Treatment Administration.....	64
4.5.1.5	Monitoring of Dose Administration .....	64
4.5.1.6	Reporting Product Complaints.....	64
4.5.2	Additional Study Medications .....	65
4.5.3	Labeling.....	65
4.5.4	Storage.....	65
4.5.5	Treatment Compliance.....	65
4.5.6	Accountability.....	65
4.6	Treatment Assignment and Blinding .....	66
4.6.1	Methods for Assigning Treatment Groups .....	66

4.6.2	Methods for Ensuring Blinding .....	66
4.6.3	Methods for Unblinding.....	67
4.6.3.1	Unblinding in the Event of a Medical Emergency .....	67
4.7	Restrictions During the Study and Concomitant Treatment(s).....	67
4.7.1	Permitted Concomitant Medications .....	67
4.7.2	Prohibited Concomitant Medications .....	68
4.8	Statistical Evaluation .....	68
4.8.1	General Considerations.....	68
4.8.2	Sample Size and Power Calculations.....	69
4.8.3	Safety.....	69
4.8.3.1	Analysis of Adverse Events.....	69
4.8.3.2	Analysis of Clinical Laboratory Parameters.....	69
4.8.3.3	Analysis of Vital Signs .....	70
4.8.3.4	Analysis of ECGs.....	70
4.8.4	Immunogenicity .....	70
4.8.5	Pharmacokinetics .....	70
4.8.6	Pharmacodynamics .....	70
4.8.7	Exploratory Endpoints .....	71
4.8.8	Timing of Analyses.....	71
5	ASSESSMENT OF SAFETY .....	71
5.1	Definition of Adverse Events .....	71
5.2	Definition of Serious Adverse Events .....	72
5.3	Definition of Adverse Events of Special Interest .....	72
5.4	Recording of Adverse Events .....	73
5.4.1	Time Period for Collection of Adverse Events.....	73
5.4.2	Follow-up of Unresolved Adverse Events.....	74
5.5	Reporting of Serious Adverse Events.....	74
5.6	Other Events Requiring Immediate Reporting .....	75
5.6.1	Overdose.....	75
5.6.2	Hepatic Function Abnormality .....	75
5.6.3	Pregnancy.....	75
5.6.3.1	Paternal Exposure .....	76
6	STUDY AND DATA MANAGEMENT .....	76
6.1	Training of Study Site Personnel .....	76
6.2	Monitoring of the Study.....	77
6.2.1	Source Data.....	77
6.2.2	Study Agreements.....	77
6.2.3	Archiving of Study Documents .....	77

6.3	Study Timetable and End of Study .....	78
6.4	Data Management .....	78
6.5	Medical Monitor Coverage .....	78
7	ETHICAL AND REGULATORY REQUIREMENTS .....	79
7.1	Ethical Conduct of the Study .....	79
7.2	Subject Data Protection .....	79
7.3	Ethics and Regulatory Review .....	79
7.4	Informed Consent .....	80
7.5	Changes to the Protocol and Informed Consent Form .....	80
7.6	Audits and Inspections .....	81
8	REFERENCES .....	82
9	CHANGES TO THE PROTOCOL .....	85
9.1	Protocol Amendment 1 .....	85

## LIST OF IN-TEXT TABLES

Table 3.1.2-1	Treatment Regimen .....	21
Table 3.2.1-1	Predicted Maximal Baseline Adjusted HDL-C and AUC of Baseline Adjusted HDL-C .....	28
Table 3.2.2-1	Predicted Baseline Adjusted HDL-C, apoA1, and CE at Early and Later Timepoints .....	32
Table 4.1.2-1	Highly Effective Methods of Contraception .....	36
Table 4.2-1	Schedule of Study Procedures (Cohorts 1-3) .....	42
Table 4.2-2	Schedule of Study Procedures (Cohort 4) .....	46
Table 4.2-3	Schedule of Study Procedures for Additional Follow-up for Subjects with ADA-positive Results (All Cohorts) .....	50
Table 4.5.1-1	Identification of Investigational Products .....	59
Table 4.5.1.3-1	Investigational Product Dose Preparation for 40 mg, 120 mg and 300 mg MEDI6012 or Placebo IV Doses .....	63
Table 4.5.1.3-2	Investigational Product IV Push Delivery Volume and Vial Usage .....	64
Table 9.1-1	Key Changes to the Protocol .....	85

## LIST OF IN-TEXT FIGURES

Figure 3.1.1-1	Study Flow Diagram and Additional Design Details .....	20
Figure 3.2.1-1	Observed MEDI6012 PK Profiles from Cohort 1 to Cohort 3 (24, 80, and 240 mg) and Population PK Model Prediction .....	24
Figure 3.2.1-2	Observed Baseline Adjusted HDL-C Profiles From Cohort 1 to Cohort 3 (24, 80, and 240 mg) and PKPD Model Prediction .....	25
Figure 3.2.1-3	Dose-response of MEDI6012 Dose Versus AUC <sub>0-96hr</sub> of Baseline Adjusted HDL-C .....	26
Figure 3.2.1-4	Predicted MEDI6012 PK Profiles .....	27

Figure 3.2.1-5	Predicted Baseline Adjusted HDL-C Profiles.....	27
Figure 3.2.2-1	Simulated HDL-C Profiles with Loading Doses of 160 to 320 mg and Weekly Maintenance Doses of 100 mg Given IV Push .....	29
Figure 3.2.2-2	Predicted MEDI6012 PK profile for Cohort 4.....	30
Figure 3.2.2-3	Simulated PD Effect on Baseline Adjusted HDL-C of a 300 mg Loading Dose followed by 150 and 100 mg Maintenance Doses on Days 3 and 10, respectively .....	31
Figure 3.2.2-4	Simulated PD Effect on Baseline Adjusted apoA1 of a 300 mg Loading Dose followed by 150 and 100 mg Maintenance Doses on Days 3 and 10, respectively. ....	31
Figure 3.2.2-5	Simulated PD Effect on Baseline Adjusted CE of a 300 mg Loading Dose followed by 150 and 100 mg Maintenance Doses on Days 3 and 10, respectively .....	32

## LIST OF APPENDICES

Appendix 1	Signatures.....	88
Appendix 2	Additional Safety Guidance.....	91
Appendix 3	National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis .....	93
Appendix 4	Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law .....	94
Appendix 5	Dietary Supplements, Prescription Drugs and Biologics Requiring or Not Requiring Wash-out.....	98

## LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ACS	acute coronary syndrome
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
ANCOVA	analysis of covariance
apoA1	apolipoprotein A1
apoB	apolipoprotein B
apoE	apolipoprotein E
AST	aspartate transaminase
AUC	area under the concentration-time curve
BP	blood pressure
CAD	coronary artery disease
CE	cholesteryl ester
CETP	cholesteryl ester transfer protein
CHD	coronary heart disease
CL	clearance
C <sub>max</sub>	maximum plasma concentration
CSR	clinical study report
CV	cardiovascular
CVD	cardiovascular disease
DEC	Dose Escalation Committee
DEHP	di-2-ethylhexyl phthalate
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FC	free cholesterol
FLD	familial LCAT deficiency
GMP	Good Manufacturing Practice
HbA1c	glycated hemoglobin
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein-cholesterol
HDL-CE	high-density lipoprotein-cholesteryl ester
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IV	intravenous(ly)
IVBP	intravenous bag protectant
IXRS	interactive voice/web response system
KO	knock out
LCAT	lecithin-cholesterol acyltransferase
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein-cholesterol
LDLr	low-density lipoprotein receptor
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or Specialized Term	Definition
nAb	neutralizing antibody
PD	pharmacodynamics
PES	polyethersulfone
PK	pharmacokinetics
PVC	polyvinylchloride
RCT	reverse cholesterol transport
rhLCAT	recombinant human lecithin-cholesterol acyltransferase
R <sub>max</sub>	maximum biomarker response
(R)T <sub>max</sub>	time to reach maximum biomarker response
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SID	subject identification
SpO <sub>2</sub>	peripheral capillary oxygen saturation
sWFI	sterile water for injection
t <sub>1/2</sub>	terminal half-life
TBL	total bilirubin
TC	total cholesterol
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TG	triglycerides
T <sub>max</sub>	time of maximal concentration
TSH	thyroid stimulating hormone
UC	unesterified cholesterol
ULN	upper limit of normal
USA	United States of America
VLDL	very low-density lipoprotein
VLDL-C	very low-density lipoprotein-cholesterol
w/v	weight by volume

## 1 INTRODUCTION

### 1.1 Disease Background

Atherosclerosis, the underlying condition of atherosclerotic cardiovascular disease (CVD), is a progressive condition associated with significant comorbidity and mortality. Excess cholesterol in arteries induces inflammation, decreases endothelium-dependent vasorelaxation, and promotes plaque instability (Tabas et al, 2007; Williams and Tabas, 1995; Williams et al, 2007; Yvan-Charvet et al, 2008). Periods of plaque instability can result in acute coronary syndrome (ACS), a spectrum of life-threatening clinical conditions that include unstable angina and non-ST- and ST-segment elevation myocardial infarction (NSTEMI and STEMI).

Plaque rupture is caused by the dissolution of the fibrous cap, the dissolution itself being the result of the release of metalloproteinases (collagenases) from activated inflammatory cells. This event is followed by platelet activation and aggregation, activation of the coagulation pathway, and vasoconstriction. Treatment for ACS is therefore focused on drugs that rapidly inhibit platelet aggregation and/or blood clot formation (Anderson et al, 2011); eg, antiplatelet agents including aspirin and the adenosine diphosphate receptor antagonists clopidogrel, prasugrel, and ticagrelor, which can be given orally, together with the intravenously (IV) administered IIb/IIIa receptor antagonists abciximab, eptifibatide, and tirofiban.

Commonly used anticoagulants include low-molecular weight heparins, thrombin inhibitors, and Factor Xa inhibitors. Drug therapies as well as percutaneous coronary interventions (PCI; balloon angioplasty and stent deployment) are focused only on the culprit lesion and do not adequately address the underlying cause of plaque vulnerability for rupture (ie, cholesterol deposition) or reduce the risk of new plaque ruptures at other sites. While chronic lipid lowering therapy with statins reduces the risk of both primary and secondary cardiovascular (CV) events by lowering plasma low-density lipoprotein-cholesterol (LDL-C), but is not thought to acutely stabilize plaque.

It has been postulated that a therapy that could rapidly remove plaque cholesterol would stabilize vulnerable plaques in ACS patients, reduce the likelihood of subsequent ischemic events, and address an important unmet medical need (Libby and Aikawa, 2003). Furthermore, this same mechanism would be expected to have similar results in the carotid and peripheral vasculature (Chen et al, 2010; Krause and Remaley, 2013; Shah, 2007).

Lecithin-cholesterol acyltransferase (LCAT) is a plasma enzyme secreted by the liver. It catalyzes the production of cholesteryl ester (CE) from free cholesterol (FC) and phosphatidylcholine (lecithin). LCAT has long been proposed to play a role in reverse cholesterol transport (RCT) (Glomset, 1968), and hence may also be important in the development of atherosclerosis (Rosenson et al, 2012). The conversion of free cholesterol on high-density lipoprotein (HDL) to CE by LCAT increases the capacity of HDL to remove additional cholesterol and maintains the gradient for cholesterol efflux from cells (Czarnecka and Yokoyama, 1996). This concept is consistent with the findings of low LCAT activity and increased pre $\beta$ -HDL in coronary heart disease (CHD) patients (Kane and Malloy, 2012; Sethi et al, 2010), although there are contradictory data on the relationship between HDL, LCAT, and CHD (Kunnen and Van Eck, 2012; Rousset et al, 2011) particularly from a large scale genome-wide association study (Haase et al, 2012). Clinical data have further suggested that low levels of LCAT may be associated with an increased incidence and/or severity of coronary artery disease (CAD) (Asztalos et al, 2000; Lamon-Fava et al, 2008; Miida et al, 1996; Sethi et al, 2010; Solajic-Bozicevic et al, 1994; Tashiro et al, 2009) and low HDL levels due to LCAT mutations increase the plaque burden in the carotid arteries (Duivenvoorden et al, 2011).

Preclinical animal models have shown that transient increased expression of LCAT can in itself substantially raise HDL-cholesterol (HDL-C) and may therefore increase RCT (Amar et al, 2009; Rousset et al, 2010). In rabbits that express endogenous cholesteryl ester transfer protein (CETP), transgenic overexpression of human LCAT has been shown to protect against diet-induced atherosclerosis (Hoeg et al, 1996). Similarly, IV administration of recombinant rabbit LCAT (rrLCAT) to wild-type rabbits has also been shown to protect against atherosclerosis (Zhou et al, 2009). Overexpression of LCAT in rabbit and monkey models shows up to a 10-fold increase in LCAT activity with a corresponding 2- to 5-fold increase in HDL-C with no adverse effects noted (Amar et al, 2009; Brousseau et al, 2000).

## 1.2 MEDI6012 Background

MEDI6012 is briefly described below. Refer to the current Investigator's Brochure for more details.

MEDI6012 (formerly ACP501) is recombinant human lecithin-cholesterol acyltransferase (rhLCAT), an approximately 60 kilodalton, glycosylated, single-chain protein consisting of 416 amino acids produced via Chinese hamster ovary cell culture. It is being explored as an acute treatment to reduce the risk of recurrent cardiovascular events as an adjunct to the standard of care in patients with ACS. MEDI6012 and ACP501 have the identical amino acid sequence and are therefore considered the same molecular entity. Improvements in the

manufacturing process resulted in greater enzymatic activity on a per-mg of protein basis and increased product- and process-related purity for MEDI6012 relative to ACP501.

### 1.3 Summary of Nonclinical Experience

[Redacted text block for Section 1.3]

### 1.4 Summary of Clinical Experience

[Redacted text block for Section 1.4]

[Redacted text block containing multiple paragraphs of obscured content]

### 1.5 Rationale for Conducting the Study

The premise of MEDI6012 clinical development is that the administration of MEDI6012 in patients with atherosclerotic CVD will upregulate mobilization of cholesterol from tissues, including cholesterol from atherosclerotic plaques in coronary, cerebrovascular, and peripheral arteries, resulting in their stabilization and a consequent decreased risk for recurrent major adverse CV events. In addition, expected improvements in HDL function

may result in the modulation of inflammation and improvements in endothelial function, effects that may contribute to a reduction in major adverse CV events.

Data from Study D5780C00002 demonstrated that MEDI6012 administered at doses of 24, 80, 240, and 800 mg IV and 80 and 600 mg SC as a single dose showed an acceptable safety profile and dose-dependent increases in HDL-C, HDL-CE, and CE. (Section 1.4). MEDI6012 is therefore being evaluated in the current study using a multiple ascending dose design to characterize the clinical PK and PD as well as safety and immunogenicity in a repeat-dose setting. This protocol is identified as a Phase 2a study since the primary PD endpoint is statistically powered for evaluation in a target subject population and builds upon the data from the Phase 2a single ascending dose study (D5780C00002).

This current Phase 2a, multiple-dose-escalation study is designed to provide PK/PD, safety, and immunogenicity data for repeat administration of MEDI6012 in a stable atherosclerotic CVD population. The subjects participating in this study will have established atherosclerosis in at least one vascular bed (coronary, carotid, or peripheral arteries). Subjects will be given three IV doses on a weekly basis. Subjects may see transient changes in lipid/lipoprotein parameters but are not expected to derive durable therapeutic benefit as they will receive only 3 doses. Subject risk will be minimized through strict eligibility criteria to avoid enrolment of unstable or high-risk subjects and by close monitoring of adverse events (AEs), laboratory parameters, vital signs, and electrocardiograms (ECGs). In addition, PK, PD, and immunogenicity will be evaluated on an ongoing basis over the course of the study.

## **1.6 Research Hypotheses**

### **1.6.1 Primary Hypotheses**

1. Repeat dosing with MEDI6012 exhibits an acceptable safety profile in subjects with stable atherosclerotic cardiovascular disease (CVD).
2. Repeat dosing with MEDI6012 results in a sustained and reversible dose-dependent response for high-density lipoprotein-cholesterol (HDL-C), cholesteryl ester (CE), and high-density lipoprotein-cholesteryl ester (HDL-CE) that allows once weekly or less frequent dosing.

### **1.6.2 Secondary Hypotheses**

1. Repeat dosing with MEDI6012 will result in a pharmacokinetic (PK) profile (lecithin-cholesterol acyltransferase [LCAT] mass and LCAT activity) that allows once weekly or more frequent dosing.

2. A regimen comprised of an initial loading dose of MEDI6012 followed by a dose at 48 hours and 1 week later will result in a rapid rise in HDL-C and apoA1 compared with no loading dose and maintenance of pharmacodynamic (PD) effect for 7 or more days.
3. Repeat dosing with MEDI6012 results in dose-dependent responses for other key pharmacodynamic (PD) biomarkers in subjects with stable atherosclerotic CVD.
4. Repeat dosing with MEDI6012 does not result in the development of neutralizing anti-drug antibodies (nAb) that cross-react with endogenous LCAT leading to decreased HDL-C.

## 2 OBJECTIVES

### 2.1 Objectives

#### 2.1.1 Primary Objective

1. The primary safety objective is to evaluate the safety of MEDI6012 following repeat dosing in subjects with stable atherosclerotic CVD over time to Day 71 (Cohorts 1-3) or Day 66 (Cohort 4).
2. The primary PD objective is to establish that repeat dosing with MEDI6012 results in a sustainable and reversible dose-dependent response for HDL-C, HDL-CE, and CE.

#### 2.1.2 Secondary Objectives

1. To establish the PK profile of MEDI6012 following repeat dose administration.
2. To establish the PD effect of MEDI6012 following an initial loading dose followed by a dose at 48 hours and 1 week later (Cohort 4 only).
3. To evaluate the effect of MEDI6012 on a range of PD biomarkers following repeat weekly dose administration.
4. To evaluate the immunogenicity potential of MEDI6012.

#### 2.1.3 Exploratory Objective

1. [REDACTED]
- [REDACTED]

## 2.2 Study Endpoints

### 2.2.1 Primary Endpoint

#### Primary Safety Endpoint

Safety and tolerability of MEDI6012 as measured by the incidence of TEAEs and TESAEs and clinically important changes in 12-lead ECG, vital signs, and clinical laboratory evaluations over time to Day 71 (Cohorts 1-3) or Day 66 (Cohort 4).

#### Primary PD Endpoint

Baseline adjusted area under the concentration time curve from time 0 to 96 hours post dose 3 ( $AUC_{0-96hr}$ ) for HDL-C, HDL-CE, and CE.

### 2.2.2 Secondary Endpoints

1. PK for MEDI6012 mass and activity.
2. Serum concentration of other key lipids and lipoproteins: CE, HDL-CE, HDL-UC, non-HDL-C, non-HDL-CE, non-HDL-UC, LDL-C, TC, apolipoprotein B (apoB), triglycerides (TG), very low-density lipoprotein-cholesterol (VLDL-C), FC, and apoA1, apoAII, apoCIII, apolipoprotein E (apoE), pre-beta1 high-density lipoprotein (pre $\beta$ 1-HDL).
3. ADA and nAb development, with concomitant decreases in HDL-C.

### 2.2.3 Exploratory Endpoint

1. 

## 3 STUDY DESIGN

### 3.1 Description of the Study

#### 3.1.1 Overview

This is a Phase 2a randomized, blinded (subject/investigator blinded, MedImmune unblinded), placebo-controlled, dose-escalation study to evaluate the PK/PD, safety and immunogenicity of repeat doses of MEDI6012 in adult subjects with stable atherosclerotic CVD. At least 32 subjects are planned to be randomized across approximately 10 study sites in the United States of America (USA) to evaluate 4 dose levels (40, 120, 300 mg, and a IV push dosing regimen that includes a loading dose of 300 mg followed by a 150 mg

maintenance dose at 48 hours and a 100 mg maintenance dose 7 days later) of MEDI6012. Subjects in Cohorts 1-3 will be administered investigational product weekly via intravenous (IV) infusions. Cohort 4 subjects will be administered investigational product using a loading dose of 300 mg (Dose 1) of MEDI6012, a second dose of 150 mg at 48 hours, followed by a maintenance dose of 100 mg 1 week later. For each cohort, 8 subjects are planned for randomization in a 6:2 ratio to receive MEDI6012 or placebo. Investigational product will be administered as a 1-hour IV infusion (Cohorts 1-3) or IV push (Cohort 4).

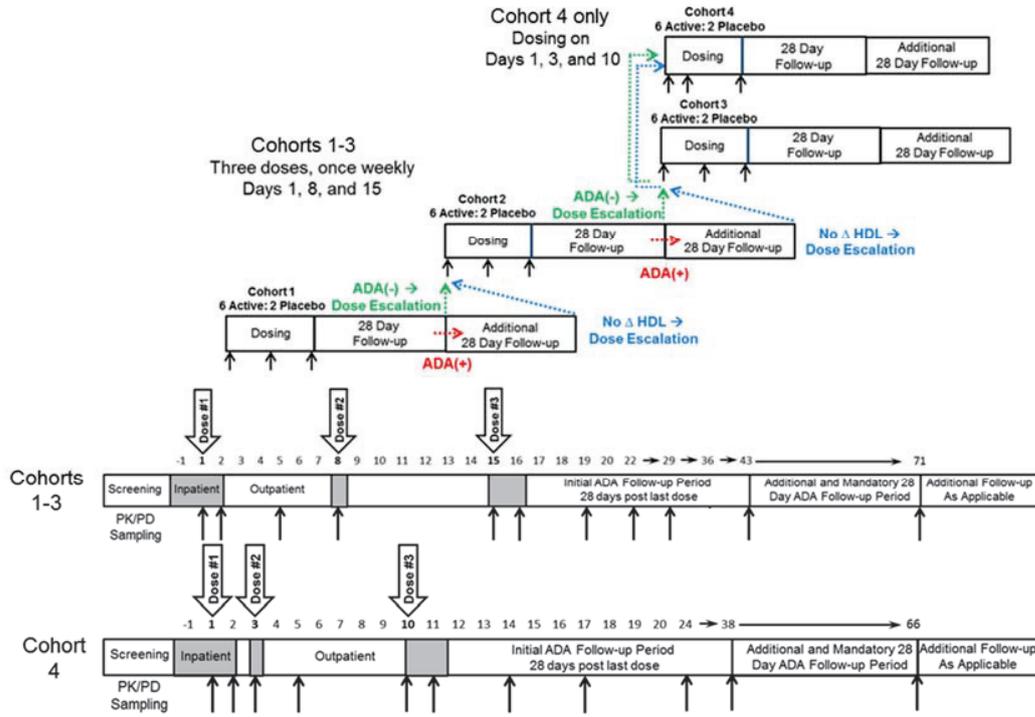
Subjects will undergo a screening period of up to 28 days. For subjects requiring a washout of dyslipidemia medication or supplement, a 56-day screening period is allowed. For Cohorts 1-3, subjects may be admitted to the study center the evening prior to randomization and first dose administration (Day -1) and prior to third dose administration (Day 15) and remain at the study center for 24-36 hours. In lieu of overnight admission, outpatient arrangements such as a hotel stay near the study center or a return to home may alternatively be provided. For Dose 2 (Day 8), subjects will be observed as inpatients for at least 8 hours following dosing. Subjects will be followed through 56 days after the third dose of investigational product (Day 71).

For Cohort 4, subjects may be admitted to the study center the evening prior to randomization and first dose administration (Day -1) and prior to third dose administration (Day 10) and remain at the study center for 24-36 hours. In lieu of overnight admission, outpatient arrangements such as a hotel stay near the study center or a return to home may alternatively be provided. For Dose 2 (Day 3), subjects will be observed as inpatients for at least 8 hours following dosing. Outpatient arrangements may be provided through Day 4. Subjects will be followed through 61 days after the third dose of investigational product (Day 66).

If a subject's Day 71 (Cohorts 1-3) or Day 66 (Cohort 4) immunogenicity sample is confirmed as ADA positive, the subject will return to the study site on Week 14 and Week 18 and approximately every 3 months (or more frequently) thereafter for additional assessments until their immunogenicity sample is no longer ADA positive, or until approximately 12 months after the Day 43 visit, whichever occurs first. If a MedImmune safety review board determines that an adverse safety signal is attributed to the ADA-positive signal, then follow up may continue beyond 12 months for subjects whose immunogenicity sample continues to be ADA positive.

Subjects will be encouraged to maintain a healthy lifestyle, including diet and exercise, during the study period.

Dose escalation will be based on safety, ADA, and PD data (HDL-C, HDL-CE, CE, LDL-C, TC, FC, apoB, and apoA1) as described in Section 3.1.3.



**Figure 3.1.1-1 Study Flow Diagram and Additional Design Details**

ADA = anti-drug antibody;  $\Delta$  HDL = change in high density lipoprotein; PD = pharmacodynamics; PK = pharmacokinetics; IV = intravenous.

Subjects may be admitted to the study center the evening prior to randomization and first dose administration (Day -1) and prior to third dose administration (Day 15 for Cohorts 1-3 or Day 10 for Cohort 4) and remain at the study center, for 24-36 hours. In lieu of overnight admission, outpatient arrangements such as a hotel stay near the study center or a return to home may alternatively be provided. For Cohort 4, outpatient arrangements may be provided through Day 4. In addition, sites may admit the evening of Day 14 for Day 15 dosing (Cohorts 1-3) or Day 9 (Cohort 4).

Subjects in Cohorts 1-3 will be administered investigational product weekly via IV infusion. Cohort 4 subjects will be administered investigational product via IV push using a loading dose of 300 mg (Day 1) of MEDI6012 followed by a 150 mg maintenance dose 48 hours later (Days 3) and a maintenance dose of 100 mg one week later (Day 10).

### 3.1.2 Treatment Regimen

Enrollment of 32 subjects is planned to evaluate 3 dose levels of MEDI6012 via IV infusions (40, 120, and 300 mg) with repeat-dose administration (Cohorts 1-3), and 300 mg loading dose followed by a 150 mg maintenance dose 48 hours later and a maintenance dose of 100 mg 1 week later all by IV push (Cohort 4; Table 3.1.2-1).

**Table 3.1.2-1 Treatment Regimen**

Cohort	Dose	Number of Doses & Dosing Frequency	Number of Subjects	Randomization
1	40 mg IV	3 once weekly doses (Days 1, 8, 15)	8	6 MEDI6012:2 Placebo
2	120 mg IV	3 once weekly doses (Days 1, 8, 15)	8	6 MEDI6012:2 Placebo
3	300 mg IV	3 once weekly doses (Days 1, 8, 15)	8	6 MEDI6012:2 Placebo
4	300 mg IV push (Day 1) 150 mg IV push (Day 3) 100 mg IV push (Day 10)	3 doses (Days 1, 3, 10)	8	6 MEDI6012:2 Placebo

IV = intravenous.

PD and PK data, as it becomes available from each cohort, will be reviewed by MedImmune and the Thrombolysis in Myocardial Infarction (TIMI) Study Group (an academic research organization part of Brigham and Women’s Hospital and affiliated with Harvard Medical School). Doses may be adjusted based on emergent safety and PD data, but the maximum exposure will not exceed 300 mg. In addition, if findings suggest that a longer dosing interval, additional subjects, or additional dose levels may need to be investigated; additional cohorts or subjects may be added to the study.

### 3.1.3 Dose Escalation

A Dose Escalation Committee (DEC) will be formed for the purpose of data review and safety monitoring, and for decisions on cohort progression as outlined in the DEC Charter. For each dose-escalation decision, the DEC will review the following data from each cohort:

- Data through 28 days after dose 3 (Day 43) including: baseline characteristics (including demographics, medical history, prior/concomitant medications), blinded safety listings assignment (including TEAEs, vital signs, ECGs including QT and QTc intervals, laboratory safety tests), subject-de-identified PD summary data (AUC for HDL-C, HDL-CE, CE, LDL-C, TC, FC, apoB, and apoA1), ADA results, and listings for select lipid variables. In addition, PK data will be reviewed as it becomes available.
- However, if there is a positive ADA 28 days after dose 3 (Day 43), dose escalation will be postponed until an additional 28 days of follow-up is complete (Day 71) with review of the following: baseline characteristics (including demographics, medical history, prior/concomitant medications), blinded safety listings assignment (including TEAEs, vital signs, ECGs including QT and QTc intervals, laboratory safety tests), subject-de-identified PD summary data (AUC for HDL-C, HDL-CE, CE, LDL-C, TC, FC, apoB and apoA1), ADA results, and listings for select lipid variables.

Each dose-escalation decision will include the data described above for all subjects in the cohort (subjects who drop out prior to this time may or may not be replaced for purposes of DEC review, at the sponsor's discretion). Cumulative data from preceding cohorts will also be reviewed.

Progression to the next higher dose will occur only if the previous dose level was deemed by the DEC to be safe and well tolerated. Dose escalation will be paused and submitted for review by a MedImmune safety review board if, within the given cohort, the DEC review determines that  $\geq 1$  subjects who received MEDI6012 have any of the following:

- Anaphylaxis
- TESAЕ or  $\geq$  Grade 3 TEAE assessed by the sponsor as related to the investigational product
- Event that in the opinion of the medical monitor and the MedImmune safety review board contraindicate further dosing
- Positive ADA result accompanied by a  $\geq 30\%$  decrease in HDL-C compared with baseline at any time point\*
- Positive ADA result with a titer  $\geq 8$  that is on the rise regardless of HDL-C levels
- Fulfill Hy's law defined as "An increase in aspartate transaminase (AST) or alanine transaminase (ALT)  $\geq 3 \times$  upper limit of normal (ULN) and total bilirubin (TBL)  $\geq 2 \times$  ULN, where no other reason can be found to explain combination of increases

\*Note: A difference of  $\geq 30\%$  is deemed to be biologically relevant because intrasubject variability for HDL-C is estimated at 2% to 5% (when factors such as diet and exercise are controlled) and HDL-C assay variability ranges from 12% to 20%. A potential mechanism for a decreased HDL-C response is the development of a nAb response against MEDI6012 that also affects endogenous LCAT activity. For this reason, in the setting of a  $\geq 30\%$  decrease in HDL or ADA titer  $\geq 8$ , the dose-escalation decision will be delayed to allow for collection and review of additional data including PK and ADA/nAb as well as safety and PD data.

Dose escalation will be paused if, within the given cohort, the DEC review determines that  $\geq 2$  subjects who received MEDI6012 have any of the following:

- An average absolute (regardless of baseline value) QTcF  $> 500$  ms, or an increase of QTcF  $> 60$  ms above baseline confirmed (persistent for  $\geq 5$  minutes) on a repeat 12-lead ECG
- Tachycardia in a subject receiving MEDI6012, defined as resting supine pulse rate  $> 125$  bpm persisting for at least 10 minutes

- Hypertension in a subject receiving MEDI6012, defined as an increase in resting supine systolic blood pressure (BP) > 40 mm Hg to above 180 mm Hg and persisting for at least 10 minutes
- Symptomatic bradycardia, with a simultaneous resting supine pulse rate < 45 bpm while awake, persisting for at least 10 minutes; or asymptomatic bradycardia defined as resting supine pulse rate < 30 bpm while awake persisting for at least 10 minutes
- Other clinically significant changes in laboratory values or safety parameters

If any of these safety criteria are met, the data will be reviewed by a MedImmune safety review board to determine whether to continue the study and/or escalate the dose. If dose-escalation stopping criteria are not met but a potential safety signal (not considered severe) indicates that further dose escalation may affect subject safety, the cohort may be expanded at the current dose level or an intermediate or lower dose level may be evaluated. Similarly, if there is a desire for efficacy signal verification, the cohort may be expanded or a cohort added.

For the purposes of DEC meetings, MedImmune staff will be unblinded while investigators, subjects, TIMI, and the contract research organization are all blinded. If a significant safety event occurs, MedImmune will determine if it occurred in a subject on MEDI6012 and the TIMI DEC members will be unblinded to participate in the DEC decision.

Following review of the data for Cohort 2 (120 mg) the DEC will trigger escalation to both Cohort 3 (300 mg IV) and Cohort 4 (300 mg IV push (Day 1) and 150 mg IV push (Day 3), and 100 mg IV push (Day 10)).

## **3.2 Study Design and Dose Rationale**

### **3.2.1 Dose Rationale for Cohorts 1-3**

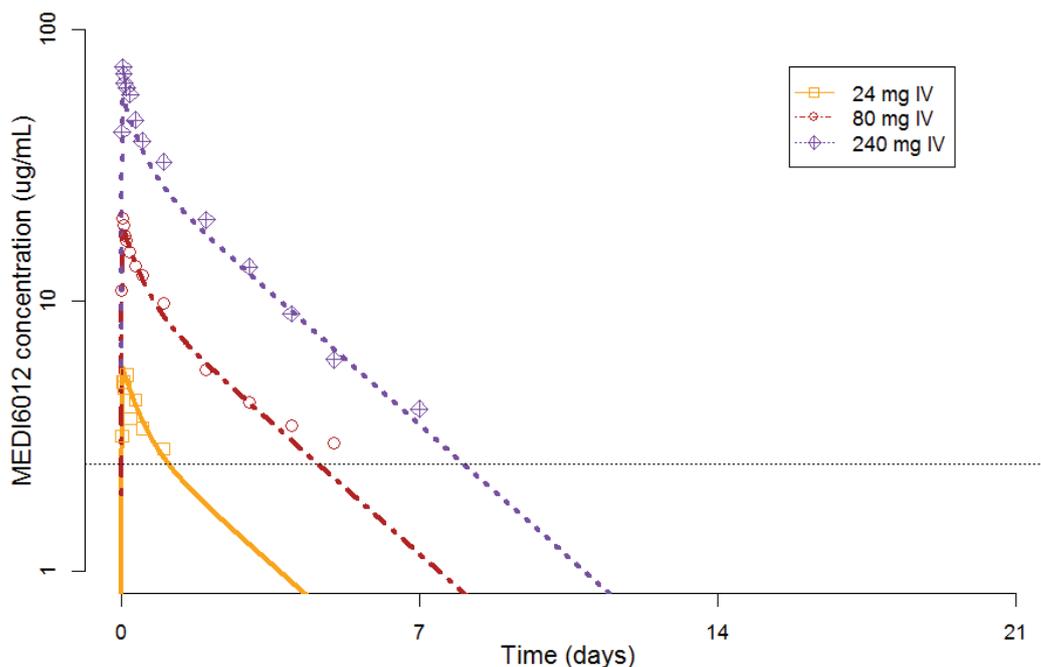
Doses for Cohorts 1-3 in this study have been selected based on preliminary PK/PD analysis that integrated Cohort 1 to Cohort 3 PK/PD data from the single-ascending dose study of MEDI6012 (D5780C00002). A dose-dependent increase in biomarkers of LCAT activity including HDL-C, HDL-CE, and CE was observed for MEDI6012 following administration of single-ascending doses (Cohort 1 to Cohort 3, 24-240 mg IV).

A mathematical model of RCT that describes the PK of MEDI6012 and relevant biomarker profiles following administration of MEDI6012 and apoA1 was developed. This model was established using data from Study ACP501-01 and from literature in the public domain. The model accounted for the following processes related to RCT: formation of discoid pre $\beta$ -HDL particles; maturation of discoid particles into spherical particles, as well as cholesterol efflux

from peripheral tissue due to HDL maturation and the concentration of  $\alpha$ -HDL with the concentration gradient between peripheral free cholesterol and free cholesterol in HDL. The model parameters were calibrated using data from the literature for studies of therapeutic intervention with pre $\beta$ -HDL particles and data from LCAT studies (Gille et al, 2014; Kujiraoka et al, 2003; Nanjee et al, 2001).

Observed PK/PD data from Cohort 1 to Cohort 3 of Study D5780C0002 were used to characterize the PK of MEDI6012 followed by updating the RCT PK/PD model.

MEDI6012 PK appeared to be linear. A 2-compartment population PK model with linear clearance (CL) was developed. The estimated CL and Vc are 88.7 mL/hour and 4.14 L, respectively. The terminal half-life ( $t_{1/2}$ ) is approximately 48 hours. The observed PK and model prediction is presented in Figure 3.2.1-1.



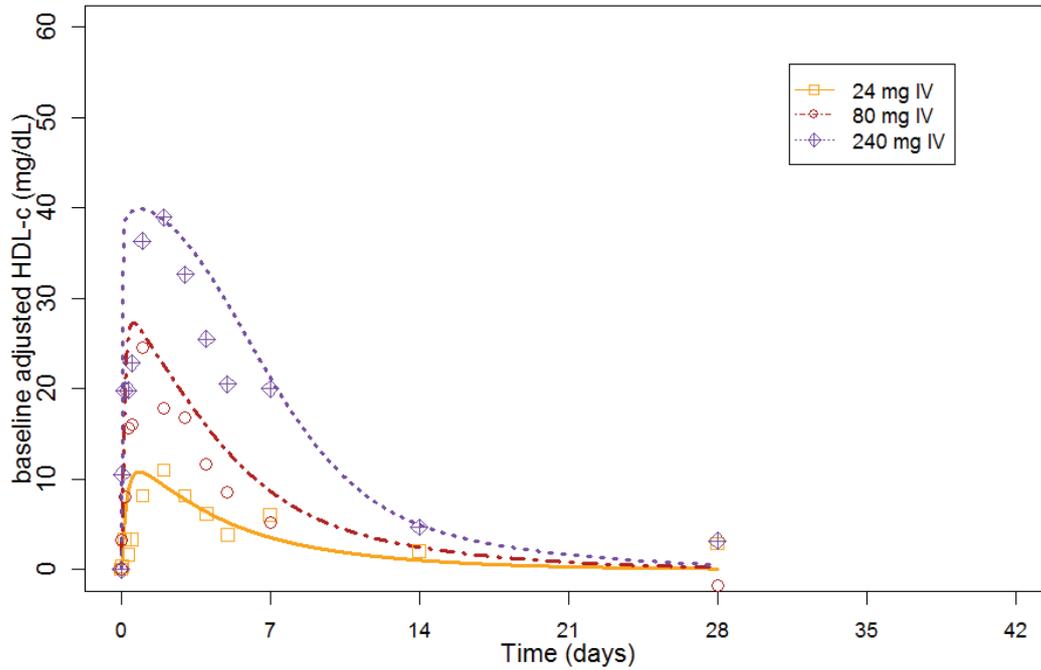
**Figure 3.2.1-1 Observed MEDI6012 PK Profiles from Cohort 1 to Cohort 3 (24, 80, and 240 mg) and Population PK Model Prediction**

IV = intravenous; PK = pharmacokinetics.

Symbol: observed MEDI6012 concentration; Solid line: population PK model prediction

Following the development of population PK model, the RCT PK/PD model was then updated and adjusted based on the observed PD data, including HDL-UC, HDL-CE, HDL-C, and CE from Cohort 1 to Cohort 3 of Study D5780C0002. The updated PK/PD model

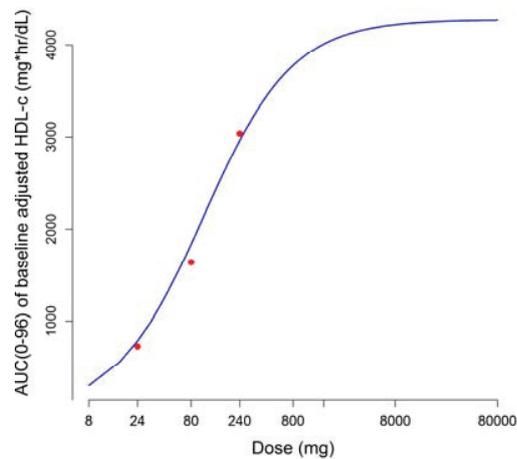
described the observed data well. [Figure 3.2.1-2](#) depicts observed HDL-C with model predictions and [Figure 3.2.1-3](#) showed the dose-response curve of MEDI6012 doses versus  $AUC_{0-96hr}$  of baseline adjusted HDL-C.



**Figure 3.2.1-2 Observed Baseline Adjusted HDL-C Profiles From Cohort 1 to Cohort 3 (24, 80, and 240 mg) and PKPD Model Prediction**

HDL-C = high-density lipoprotein cholesterol; IV = intravenous; PD = pharmacodynamics; PK = pharmacokinetics.

Symbol: observed data; solid line: model prediction.



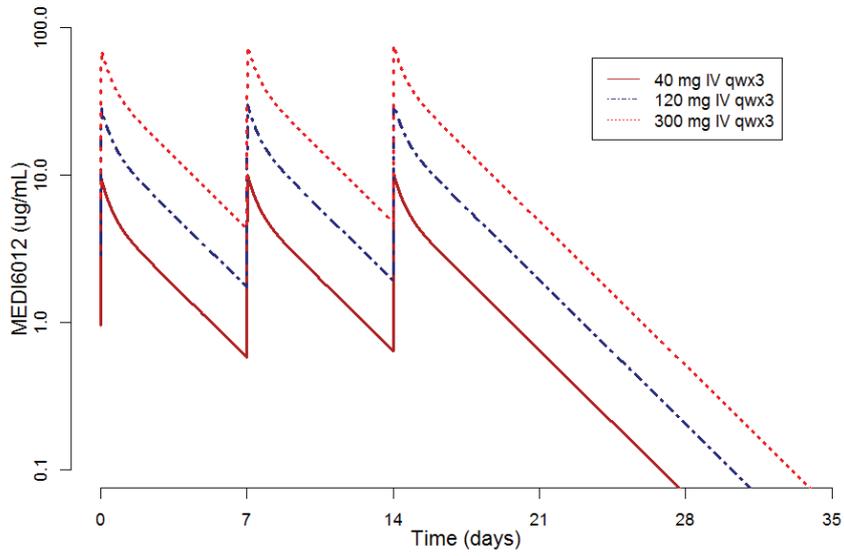
**Figure 3.2.1-3 Dose-response of MEDI6012 Dose Versus AUC0-96hr of Baseline Adjusted HDL-C**

AUC<sub>0-96hr</sub> = area under the concentration-time curve from 0-96 hours; HDL-C = high-density lipoprotein-cholesterol

Legend: Red dots = observed data; blue line = model prediction

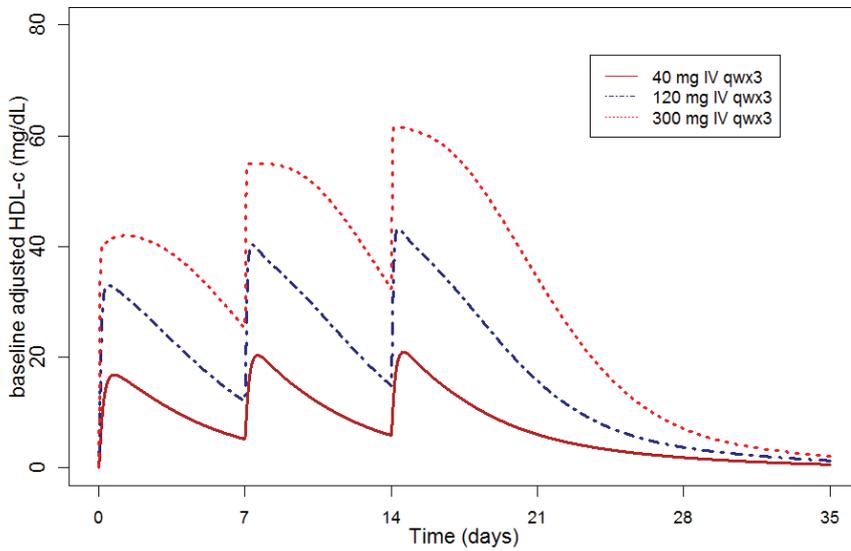
Simulations utilizing this PK/PD model were performed based on the estimated PK/PD parameters to select doses for Cohorts 1-3 in this study that can characterize MEDI6012 PK and the range of PD effects when administering MEDI6012 repeatedly. The doses proposed for Cohort 1-3 of this study are 40, 120, and 300 mg via three-weekly IV infusions.

Predicted MEDI6012 PK and HDL-C profiles following the proposed dose regimens for Cohort 1-3 of this study are shown in [Figure 3.2.1-4](#) and [Figure 3.2.1-5](#). The estimated maximal baseline adjusted HDL-C and AUC of baseline adjusted HDL-C are presented in [Table 3.2.1-1](#).



**Figure 3.2.1-4 Predicted MEDI6012 PK Profiles**

IV = intravenous; PK = pharmacokinetic; qwx3 = 3 weekly doses.



**Figure 3.2.1-5 Predicted Baseline Adjusted HDL-C Profiles**

HDL-C = high-density lipoprotein cholesterol; IV = intravenous; qwx3 = 3 weekly doses.

**Table 3.2.1-1 Predicted Maximal Baseline Adjusted HDL-C and AUC of Baseline Adjusted HDL-C**

MEDI6012 Doses	Maximal Baseline Adjusted HDL-C Following Dose #3	AUC <sub>0-96hr</sub> of Baseline Adjusted HDL-C (mg*hr/dL)	AUC <sub>336-432hr</sub> of Baseline Adjusted HDL-C (mg*hr/dL)
40 mg IV × 3	20.9	1250	1520
120 mg IV × 3	43.1	2620	3440
300 mg IV × 3	61.7	3840	5600

AUC = area under the concentration-time curve; AUC<sub>0-96hr</sub> = area under the concentration-time curve from 0 to 96 hours; AUC<sub>336-432hr</sub> = area under the concentration-time curve from 336 to 432 hours; HDL-C = high-density lipoprotein-cholesterol; IV = intravenous.

Administration of 3 repeat doses in Cohorts 1-3 was selected for the dose range of 40 to 300 mg to support future clinical studies in which repeat-dose administration of MEDI6012 within this range are planned. Three once weekly doses provide sufficient PK/PD data for safety evaluation (including immunogenicity) and to characterize the PK/PD relationship prior to selecting the appropriate dose levels to evaluate in future studies.

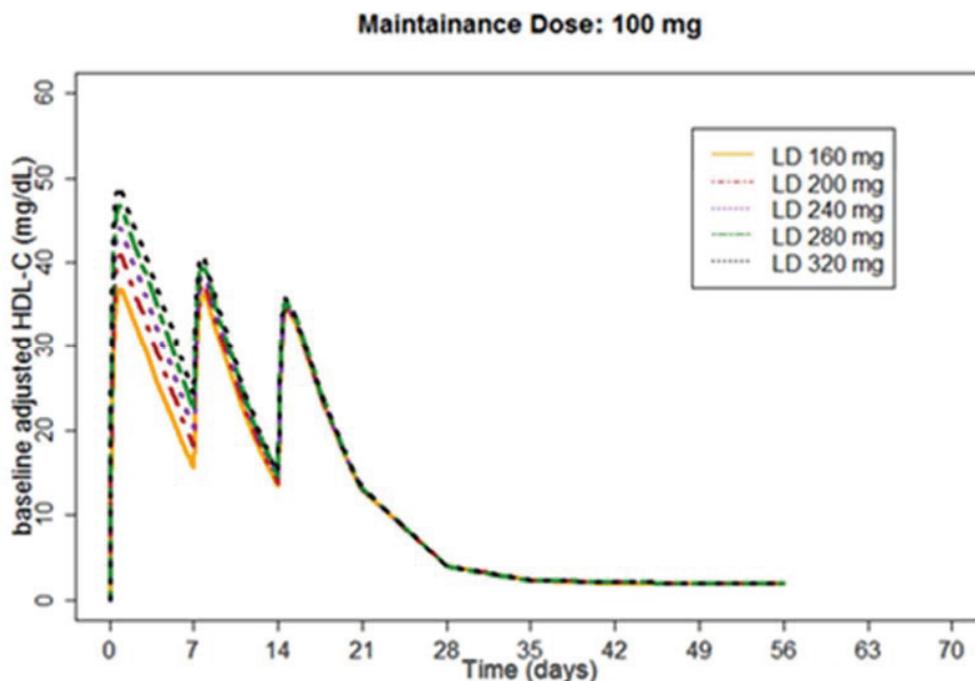
This also informs the IV bioavailability of MEDI6012 in atherosclerotic CVD patients and potentially can be applied in other indications as well.

### 3.2.2 Dose Rationale for Cohort 4

PD observations from the single-ascending dose study of MEDI6012 (D5780C00002) and Cohorts 1 and 2 from the current study (D5780C00005) have demonstrated that the rate of increase of HDL-C and apoA1 are dose dependent. For future studies in ACS and acute MI subjects, maximizing the rate of increase of HDL-C and apoA1 following the first and second dose, may allow a coupling of the anti-atherosclerotic effects of enhanced reverse cholesterol transport with the cardioprotective effects of HDL-C and apoA1 resulting in multiple benefits for CHD patients (Gordts et al, 2013; Kalakech et al, 2014; Marchesi et al, 2004; Richart et al, 2015; Theilmeier et al, 2006). Therefore, Cohort 4 is being added to the protocol in order to test IV push administration of a loading dose followed by 48 hour and then weekly maintenance doses.

The loading dose and maintenance doses for Cohort 4 have been selected based on PK/PD analysis that integrated PK/PD data from the single-ascending dose study of MEDI6012 (D5780C00002) and PD data from the current study (D5780C00005). Simulations utilizing the RCT PK/PD model were performed based on the estimated PK/PD parameters to select doses for Cohort 4 in this study that can characterize MEDI6012 PK and the range of PD effects when administering MEDI6012 with loading and maintenance doses administered via IV push.

The PD effect of increasing loading doses of MEDI6012 (160, 200, 240, 280, and 320 mg) administered by IV bolus over 1 minute were simulated followed by weekly maintenance doses of 80, 100, 120, and 160 mg. From these simulations, it was noted that HDL-C decreases by over 50% over the first week [Figure 3.2.2-1](#).

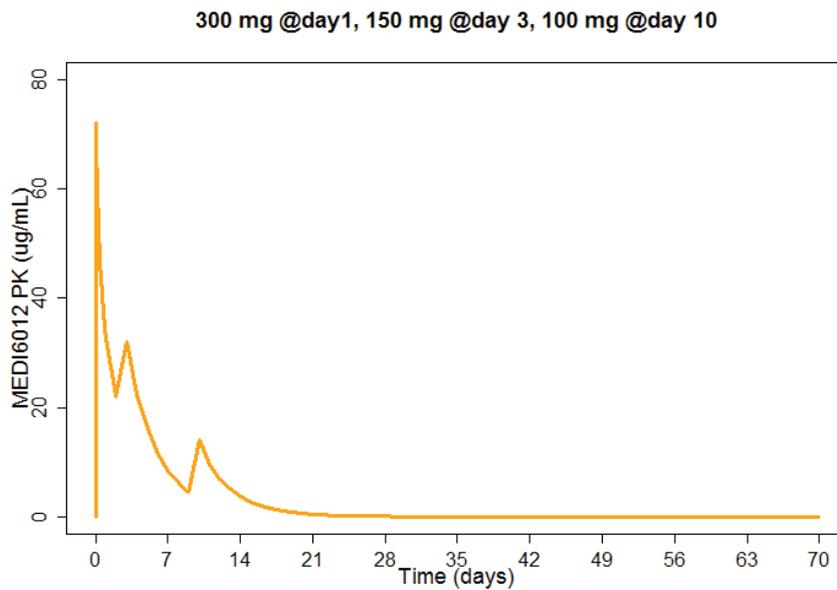


**Figure 3.2.2-1 Simulated HDL-C Profiles with Loading Doses of 160 to 320 mg and Weekly Maintenance Doses of 100 mg Given IV Push**

HDL-C = high-density lipoprotein- cholesterol; IV = intravenous; LD = loading dose

Based on the PK/PD modeling and simulation, the doses proposed for Cohort 4 are 300 mg loading dose on Day 1, 150 mg maintenance dose on Day 3, and 100 mg maintenance dose on Day10. A dosing regimen with a loading dose followed by maintenance doses on Day 3 and 10, respectively, was considered as the optimal dosing regimen that sustain elevations of HDL-C for 1 week. Day 3 was chosen since most acute MI patients are hospitalized for  $\geq 48$  hours.

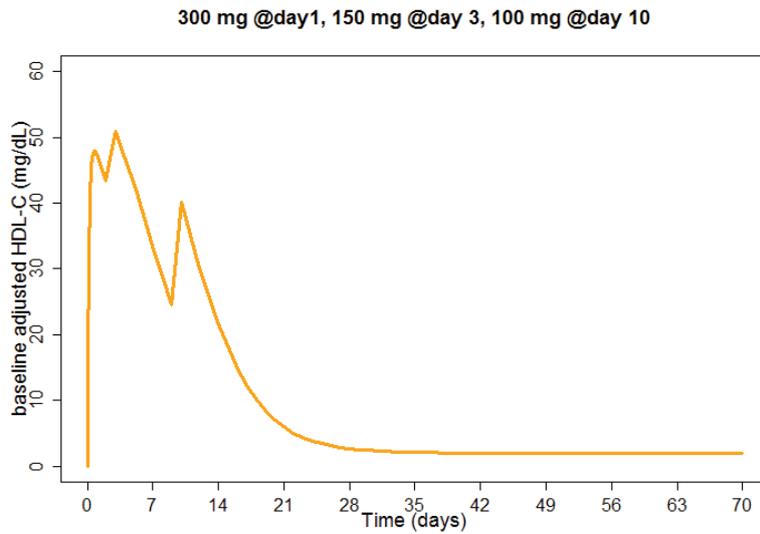
Predicted MEDI6012 PK profiles following the proposed dose regimen for Cohort 4 of this study are shown in [Figure 3.2.2-2](#). The estimated baseline adjusted HDL-C, apoA1, and CE are presented in [Table 3.2.2-1](#).



**Figure 3.2.2-2 Predicted MEDI6012 PK profile for Cohort 4**

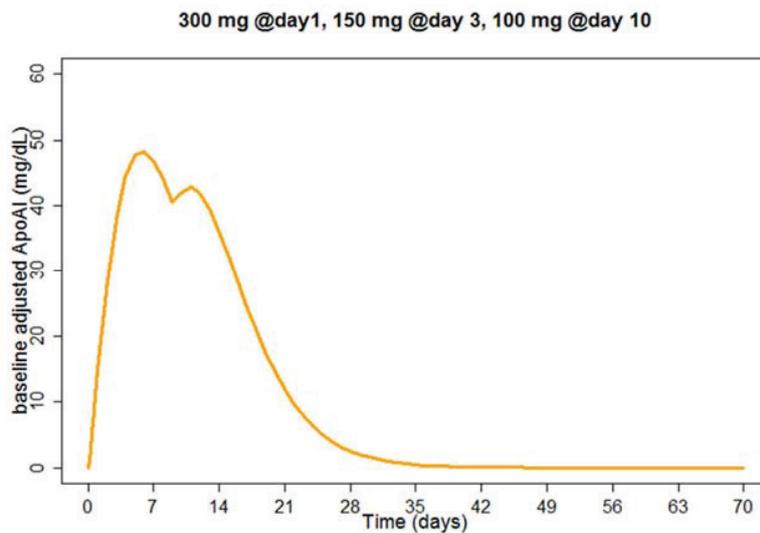
PK = pharmacokinetic

The baseline adjusted HDL-C profiles over time is demonstrated in [Figure 3.2.2-3](#). This regimen resulted in baseline adjusted HDL-C levels >30 mg/dL for greater than 1 week. The first week following acute MI is critical in regards to cardioprotective and vasculoprotective aspects of therapy. In addition, this regimen results in early apoA1 levels near at the peak seen with larger doses (up to 800 mg IV) used in the single-ascending dose study of MEDI6012 (D5780C00002) and therefore maintains apoA1 levels for > 1 week ([Figure 3.2.2-4](#)). The 100 mg maintenance dose on Day 10 was selected because it maintains cholesteryl ester in the system without accumulation of cholesteryl ester ([Figure 3.2.2-5](#)) and is being tested to determine if this is an appropriate maintenance dose for longer term dosing of MEDI6012 for future studies.



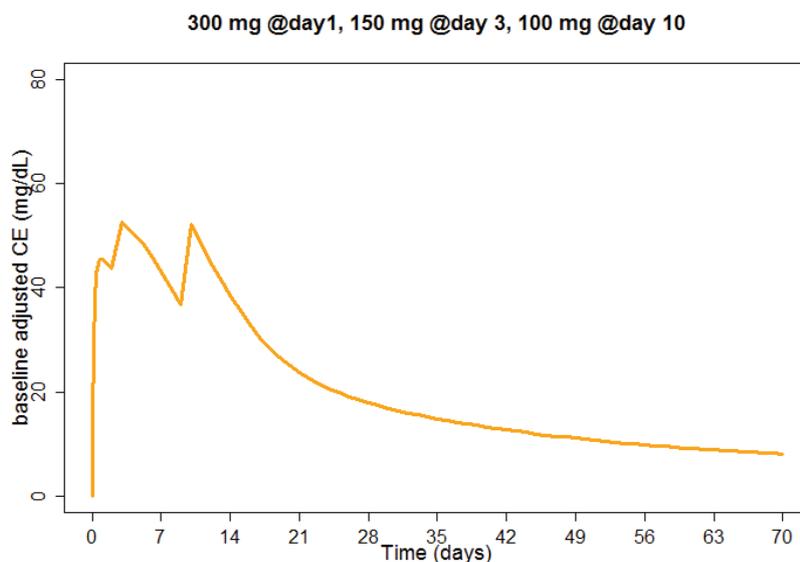
**Figure 3.2.2-3 Simulated PD Effect on Baseline Adjusted HDL-C of a 300 mg Loading Dose followed by 150 and 100 mg Maintenance Doses on Days 3 and 10, respectively**

HDL-C = high-density lipoprotein-cholesterol



**Figure 3.2.2-4 Simulated PD Effect on Baseline Adjusted apoA1 of a 300 mg Loading Dose followed by 150 and 100 mg Maintenance Doses on Days 3 and 10, respectively.**

ApoA1 = apolipoprotein A1; PD = pharmacodynamic



**Figure 3.2.2-5 Simulated PD Effect on Baseline Adjusted CE of a 300 mg Loading Dose followed by 150 and 100 mg Maintenance Doses on Days 3 and 10, respectively**

CE = cholesterol ester; PD = pharmacodynamic

**Table 3.2.2-1 Predicted Baseline Adjusted HDL-C, apoA1, and CE at Early and Later Timepoints.**

Time	Baseline Adjusted HDL-C	Baseline Adjusted apoA1	Baseline Adjusted CE
3 hr post dose #1	26.5	0.741	24.1
6 hr post dose #1	38.2	2.38	35.3
12 hr post dose #1	46.5	6.56	43.5
Post dose #1 maximum	47.9	27.1	45.5
Post dose #2 maximum	50.9	48.3	52.7
Post dose #3 maximum	40.3	43.0	52.2

HDL-C = high-density lipoprotein-cholesterol; apoA1 = apolipoprotein A1, CE = cholesteryl ester.

In summary, the proposed dose regimens following three doses of MEDI6012 are expected to be well tolerated, and the collected PK/PD data will be appropriate to fulfill the objectives of this study. The follow-up duration of 4 weeks after dosing is deemed appropriate to evaluate the reversibility of potential safety findings and to characterize the potential immunogenicity of MEDI6012 when serum concentration (PK mass) has completely cleared and PD biomarkers return to baseline values. An additional duration of 4 weeks beyond the initial 4 weeks is appropriate in ADA positive subjects to ensure there is not a decrease in HDL-C as a result of an ADA/nAb.

### **3.2.3 Rationale for Study Population**

The study population consists of adults with a history of documented atherosclerotic CVD who are clinically stable on current lipid lowering therapy with a statin. This population is similar to the study population evaluated in the single ascending dose study of MEDI6012. However, we will be expanding the population to include asymptomatic carotid artery disease and peripheral artery disease. This population strikes the best balance to permit safety, PK, and PD assessment of MEDI6012 in subjects with established atherosclerosis, the target population for subsequent clinical development, but who are clinically stable (lower safety risk) with less fluctuation in biomarker levels to enable robust PK/PD decisions. Subjects with unstable atherosclerotic CVD will be excluded.

Subjects will be required to be on a stable statin regimen as is the standard of care for atherosclerotic disease, with LDL-C levels  $\leq 160$  mg/dL at screening. This requirement is to avoid enrolling subjects with genetically low LDL receptor concentration (and thus high or very high baseline LDL-C) and to provide a more homogeneous population against which to evaluate the lipid/lipoprotein changes of interest.

Similarly, subjects with high baseline HDL-C values ( $> 60$  mg/dL for men,  $> 65$  mg/dL for women) will be excluded to provide consistency among the study subjects for the upward movement of HDL-C levels that will facilitate the selection of doses to take forward into the next study.

### **3.2.4 Rationale for Endpoints**

#### **3.2.4.1 Rationale for Primary Endpoint**

The primary safety endpoints are considered standard safety measures.

The primary PD endpoints are HDL-C, HDL-CE, and CE, which will be analyzed as baseline-adjusted  $AUC_{0-96hr}$  following the third dose of MEDI6012. Since rhLCAT esterifies free cholesterol in HDL, it is expected that the effectiveness of MEDI6012 will correlate with changes in HDL-C, HDL-CE, and CE levels. This relationship has held true for ACP501 studies in both stable CAD subjects and in the patient with FLD, as well as the more recent SAD study in stable CAD subjects receiving MEDI6012. This is also supported by the MEDI6012 cynomolgus monkey toxicology study (normal animals with intact endogenous rhLCAT and high levels of HDL-C) that showed a robust and transient increases in HDL-C following MEDI6012 infusion.

### 3.2.4.2 Rationale for Other Key PD Endpoints

Lipoproteins and lipid panel components were selected because movement of these markers, as a result of MEDI6012 dosing, provide supporting evidence of increased activity on the RCT system in the single ascending dose study. TC represents the sum of unesterified and esterified cholesterol on all plasma lipoproteins. HDL-C represents the amount of cholesterol present in HDL particles, which can be further split into HDL-UC and HDL-CE fractions. Through its enzymatic activity, MEDI6012 is expected to result in increases in HDL-C, the primary PD biomarker. TC, and LDL-C further assess the effects of rhLCAT on RCT and are therefore identified as secondary PD endpoints.

### 3.2.4.3 Rationale for PK Endpoints

Serum concentration of MEDI6012 (mass) will be used to characterize MEDI6012 exposure. The PK may also be used to develop dose-exposure-PD response relationships to help inform dose selection for future clinical studies. Serum LCAT activity will provide an alternative measure to LCAT mass in establishing the relationship between PK and PD.

### 3.2.4.4 Rationale for Immunogenicity Endpoints

Formation of ADA against MEDI6012 is a potential risk. The ADA potential of this compound will be assessed, and formation of any nAb will also be characterized and reported separate from the CSR. In addition, HDL-C levels will be monitored in subjects with a positive ADA/nAb result. See Section 4.3.5 for further details.

### 3.2.4.5 Rationale for Exploratory PD Endpoints

[Redacted content]



## 4 MATERIALS AND METHODS

### 4.1 Subjects

#### 4.1.1 Number of Subjects

At least 32 subjects are planned as described in Section 3.1.2.

#### 4.1.2 Inclusion Criteria

1. Adult male and female subjects of non-childbearing potential aged 60 through 80 years at the time of screening who are capable of providing informed consent prior to screening and any protocol-related procedures.
2. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act [HIPAA] in the USA) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.
3. Ability to complete and meet all eligibility requirements for randomization within 28 days of informed consent (or 56 days for subjects who require washout of a concomitant medication)
4. A diagnosis of stable atherosclerotic CVD documented prior to screening:
  - a. Coronary artery disease defined as a history of prior myocardial infarction, coronary revascularization, history of coronary atherosclerosis based on invasive or non-invasive imaging, and/or abnormal stress testing diagnostic of CAD.
  - b. Carotid artery disease (extracranial ICA stenosis) defined as evidence of carotid atherosclerosis by carotid imaging, or history of percutaneous or surgical carotid revascularization
  - c. Peripheral artery disease defined as ankle-brachial index  $< 0.90$  and claudication, or prior peripheral revascularization for ischemia, or evidence of lower extremity (below the inguinal ligament) atherosclerosis on invasive or noninvasive imaging
5. Currently receiving statin as standard of care, at a stable dose for  $\geq 6$  weeks prior to screening and intended to remain at a stable dose throughout the study duration.
6. Nonsterilized males who are sexually active with a female partner of childbearing potential must use condom and spermicide from Day 1 through the end of their participation in the study. Because male condom and spermicide is not a highly effective contraception method it is strongly recommended that female partners of a male study subjects also use a highly effective method of contraception throughout this period (see [Table 4.1.2-1](#)).

**Table 4.1.2-1 Highly Effective Methods of Contraception**

<ul style="list-style-type: none"><li>• Tubal occlusion</li><li>• Copper T intrauterine device</li><li>• Levonorgestrel-releasing intrauterine system (eg, Mirena<sup>®</sup>)</li><li>• Medroxyprogesterone injections (eg, Depo-Provera<sup>®</sup>)</li><li>• Etonogestrel implants (eg, Implanon<sup>®</sup>, Norplan<sup>®</sup>)</li><li>• Combined pills</li><li>• Norelgestromin/ethinyl estradiol transdermal system (eg, Ortho Evra<sup>®</sup>)</li><li>• Intravaginal device (eg, NuvaRing<sup>®</sup>)</li><li>• Cerazette<sup>®</sup> pill</li></ul>
--

### 4.1.3 Exclusion Criteria

1. Unstable cardiovascular conditions within 3 months prior to screening, including ACS, stroke or transient ischemia attack, critical limb ischemia, non-elective arterial revascularization, life-threatening arrhythmias, or heart failure hospitalization.
2. Elective arterial revascularization (in any vascular territory) in the past 1 month.
3. Any planned arterial revascularization (coronary, peripheral or carotid).
4. Canadian Cardiovascular Society Class III or higher angina pectoris, New York Heart Association (NYHA) Class III or IV congestive heart failure or treatment with advanced therapies (cardiac transplant, ventricular assist device, cardiac resynchronization therapy, and/or chronic IV inotropic support), or severe valvular heart disease.
5. Body mass index < 18 or > 45.
6. Lipid measurements with any of the following:
  - a. Triglycerides > 500 mg/dL
  - b. LDL-C > 160 mg/dL (by direct measure)
  - c. HDL-C > 60 mg/dL for males or > 65 mg/dL for females
7. Clinically significant vital sign abnormalities at screening or on Day -1:
  - a. Systolic blood pressure (BP) < 90 or >160 mm Hg
  - b. Diastolic BP > 100 mm Hg
8. Females currently breastfeeding or of childbearing potential. (Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or those who are not postmenopausal (defined as 12 months with no menses without an alternative medical cause and a follicle-stimulating hormone level in the central laboratory's normal range for post-menopausal phase is required at screening).
9. Any clinically significant ECG that may interfere with the interpretation of serial ECG and QT interval changes at screening (following central read) or Day -1 (as judged by the investigator), including but not limited to:
  - a. Prolonged QTcF > 450 milliseconds (based on the mean of triplicate ECGs) or family history long QT syndrome

- b. PR(PQ) interval < 120 milliseconds (subjects with PR 110-119 milliseconds are acceptable if there is no evidence of ventricular pre-excitation)
- c. PR(PQ) interval > 240 milliseconds or history of Mobitz Type II second degree or third degree atrioventricular (AV) block
- d. QRS > 160 milliseconds

Note: subjects may be retested for ECG parameters one time only if, in the opinion of the investigator, the values are not representative of the subject. Any further testing beyond this must be discussed with the medical monitor in advance.

- 10. Use of lipid-lowering medications, with the exception of statins, and the following dietary supplements:  $\geq 2$  grams/day of fish oil ( $\geq 2$  grams/day DHA and EPA combined),  $\geq 30$  grams/day of flaxseed oil or ground flaxseed, red yeast extract, > 100 mg/day of niacin. (At the investigator's discretion, subjects may undergo a 4-week washout period of any exclusionary lipid-lowering agents with the expectation that post-washout lipid levels will be rechecked and acceptable per above criteria)
- 11. History of any of the following:
  - a. Documented homozygous familial hypercholesterolemia
  - b. Documented genetic disorder of cholesterol metabolism
  - c. Chronic kidney disease defined by estimated glomerular filtration rate < 30 mL/min/1.73 m<sup>2</sup> by the modification of diet in renal disease equation, or end stage renal disease treated with kidney transplant or renal replacement therapy
  - d. History of clinically overt chronic liver disease or biochemical evidence of liver disease (eg, AST or ALT > 1.5  $\times$  ULN and/or total bilirubin > ULN (unless due to Gilbert's syndrome))
  - e. Poorly controlled endocrine disorder including: 1) Type 1 or Type 2 Diabetes Mellitus with glycated hemoglobin [HbA1c] > 10% as assessed at screening or 2) uncontrolled thyroid disorder defined as thyroid stimulating hormone (TSH) > 1.5  $\times$  ULN and abnormal free T4; subjects with thyroid deficiency should have received a stable dose of thyroid hormone for > 6 weeks prior to screening
  - f. Current or previous use of systemic corticosteroids within 28 days prior to screening. Topical, intra-articular, intranasal, inhaled, and ophthalmic steroid therapies are allowed
  - g. History of severe infection or ongoing febrile illness within 30 days of screening, or a history of a chronic viral illness including hepatitis B or C virus, or human immunodeficiency virus (HIV). In the case of a positive hepatitis C (HCV) antibody test, a second antibody test is allowed and will qualify subject if negative.
  - h. History of active malignancy within 5 years (subjects with non-melanotic skin cancer may be included)
  - i. Any other disease or condition or laboratory value that, in the opinion of the investigator or medical monitor, would place the subject at an unacceptable risk or interfere with the evaluation of the investigative product. Note: for abnormal lab values, subjects may be re-assessed one time only if, in the investigator's judgment, the values are not representative of the subject; any further re-test beyond this must be discussed with the medical monitor in advance.

12. History of alcohol or recreational substance abuse within the past 6 months. (A positive drug screen is exclusionary. However, subjects with a documented medical need or prescription can be included at the discretion of the Principal Investigator [PI]).
13. Known allergy/hypersensitivity to any component of the investigational product formulation, other biologics, IV infusion equipment, plastics, adhesive or silicone, history of infusion site reactions with IV administration of other medicines, or ongoing clinically important allergy/hypersensitivity as judged by the investigator.
14. Subjects who are legally institutionalized
15. An employee or close relative of an employee of the sponsor, the contract research organization, or the study site, regardless of the employee's role.
16. Previous Exposure to rhLCAT
17. Concurrent enrollment in another clinical study of any investigational drug therapy or use of any biologics within 6 months prior to screening or within 5 half-lives of an investigational agent or biologic, whichever is longer.

If the screening assessments are not considered to be representative of the usual status of the subject's health by the investigator, or if one or more exclusion criteria are considered temporary or from a reversible condition, repeat screening assessments to establish eligibility will be permitted on one occasion, at the discretion of the investigator. Any further screening will require permission from the medical monitor. Screening values and assessments will be made by the central laboratory/reader; Day -1 assessments will be performed by local testing.

#### **4.1.4 Subject Enrollment and Randomization**

Study participation begins (ie, a subject is "enrolled") once written informed consent is obtained. Once informed consent is obtained, a subject identification (SID) number will be assigned by a central system (eg, an interactive voice/web response system [IXRS]), and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The SID number will be used to identify the subject during the screening process and throughout study participation, if applicable.

A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria and/or are not randomized), including the reason(s) for screening failure.

Subjects who fail to meet the inclusion/exclusion criteria (ie, screening failures) should not be randomized or receive investigational product.

#### 4.1.5 Withdrawal from the Study

Subjects are at any time free to stop study treatment or completely withdraw from the study (investigational product and assessments), without prejudice to further treatment. If complete withdrawal of consent is established, then no further study visits or data collection should take place. However, subjects who wish to discontinue investigational product only are expected to remain in the study for the follow-up of AEs and vital status.

#### 4.1.6 Discontinuation of Investigational Product

The investigator and/or medical monitor may determine that an individual subject will not receive any further investigational product if any of the following occur in the subject in question:

1. Clinically significant progression of atherosclerotic CVD (ie, progressive or unstable angina, myocardial infarction, urgent coronary revascularization, non-fatal stroke, transient ischemic attack, hospitalization for unstable angina or heart failure, urgent carotid revascularization) or other major cardiovascular event.
2. Any of the following liver function abnormalities:
  - ALT or AST  $> 8 \times$  ULN
  - ALT or AST  $> 5 \times$  ULN for more than 2 weeks
  - ALT or AST  $> 3 \times$  ULN and total bilirubin  $> 2 \times$  ULN; see [Appendix 4](#) for additional details regarding reporting of subjects with ALT or AST  $> 3 \times$  ULN and total bilirubin  $> 2 \times$  ULN with unknown etiology (ie, Hy's law cases)
  - ALT or AST  $> 3 \times$  ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ( $> 5\%$ )
3. Severe adverse immune reaction (eg, immune complex disease, infusion site reaction) assessed by the investigator as intolerable and related to investigational product
4. Any other AE that, in the opinion of the investigator or the sponsor, contraindicates further dosing
5. After initial dosing, there exists a significant safety issue by which the subject is determined to have previously met one or more of the exclusion criteria or failed to meet all of the inclusion criteria for study participation
6. Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal (eg, refusal to adhere to scheduled visits)
7. Withdrawal of consent from further treatment with investigational product or lost to follow-up
8. Pregnancy in any female subject

Subjects who receive any amount of investigational product will be followed for protocol-specified assessments including follow-up of any AEs unless it is confirmed that consent is withdrawn. If a subject that received at least one dose of investigational product

becomes lost to follow-up, starts an alternative treatment, or is enrolled in another clinical trial, then at least vital status will be assessed at the end of the trial (Section 4.1.5)

#### **4.1.7 Replacement of Subjects**

Subjects who withdraw from the study or do not have 96 hour post-dose 3 follow-up sample (Day 19 for Cohorts 1-3 and Day 14 for Cohort 4) may be replaced, if deemed necessary by the medical monitor, to ensure that safety, PK, and PD data are collected on a sufficient number of subjects. If a subject who does not meet all eligibility criteria is randomized and dosed in error, the investigator should inform the medical monitor immediately. A determination whether or not to replace the subject will be made jointly between the investigator and medical monitor.

Subjects may be rescreened only once unless otherwise approved by the study sponsor.

#### **4.1.8 Withdrawal of Informed Consent for Data and Biological Samples**

##### **Biological Samples Obtained for the Main Study**

Study data are protected by the use of an SID number, which is a number specific to the subject. The investigator is in control of the information that is needed to connect a study sample to a subject. A subject's consent to the use of data does not have a specific expiration date, but the subject may withdraw consent at any time by notifying the investigator. If consent is withdrawn, any samples collected prior to that time may still be given to and used by the sponsor but no new data or samples will be collected unless specifically required to monitor safety of the subject.

##### **Samples Obtained for Future Research**

Samples obtained for future research may be used for potential future analysis [REDACTED]

[REDACTED]  
[REDACTED]  
[REDACTED] Blood volumes and aliquots would need to be adjusted accordingly. Samples obtained for future research will be labeled with a sample identification number, but will not be labeled with personal identifiers such as the subject's name. A file linking this sample identification number with the SID number will be kept in a secure place at the sponsor with restricted access. If the subject withdraws consent for participating in the future research, this link will allow the sponsor to locate the subject's sample and destroy it. The coding of samples and results is to ensure that these research results are kept confidential by keeping the subject's identity and these results separate.

If the subject consents to have his/her samples used for future research, this additional research may not start immediately and may start at any time during the storage period. The subject's sample(s) will be aliquoted and stored by the sponsor with similar samples from other subjects at a secure central laboratory. The subject's samples will not be kept for more than 25 years after the end of the study in which they were collected. If the subject chooses not to allow his/her study samples to be used for future research, the samples will be destroyed by the sponsor once they are no longer required for the main study.

If consent is withdrawn after a sample has been taken, but before the subject's sample is sent to the sponsor for future research, the investigator will arrange to have it destroyed. If consent is withdrawn after the subject's sample(s) have been sent to the sponsor for future research, the sponsor and the investigator will ensure that these sample(s) are destroyed unless the identification number has been removed and the subject can no longer be linked to any sample(s). However, if the subject's samples have already been used for research, the sponsor is not required to destroy results of this research. In this case only the remaining sample(s) will be destroyed.

## **4.2 Schedule of Study Procedures**

Table 4.2-1 (Cohorts 1-3) and Table 4.2-2 (Cohort 4) shows all procedures to be conducted in subjects during the study. Table 4.2-3 shows procedures to be conducted for subjects who require additional follow-up due to an ADA-positive result at the Day 71 (Cohorts 1-3) or Day 66 (Cohort 4) visit.

Subjects must refrain from strenuous exercise and alcohol consumption for approximately 48 hours prior to any study visit. Mild to moderate exercise is encouraged.

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the blood draws should occur last.

For samples that require fasting, a minimum of 6 hours of fasting is required.

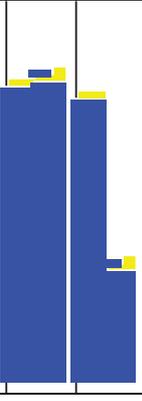
**Table 4.2-1 Schedule of Study Procedures (Cohorts 1-3)**

Study Period	Screening		Treatment Period								Follow-up				
	Day -28 (Day -56) to Day -2 <sup>a</sup>	Day -1	V1		V2	V3		V4		V5	V6	V7	V8	V9	
			Day 1 (Dose 1)	Day 8 (Dose 2)		Day 15 (Dose 3)	Day 16								
Time point/Procedure			0 hr	EOI 12 hr	D5	0 hr	EOI 12 hr	0 hr	EOI 12 hr						
Main study informed consent / assignment of SID number	X														
Future use informed consent (optional)	X														
Medical history (including cardiovascular history)	X														
Body weight	X	X												X	
Height	X														
Physical examination	X	X	X			X				X	X	X	X	X	
Vital signs (BP, respiratory rate, pulse, pulse oximetry, body temperature) <sup>b</sup>	X	X	X			X				X	X	X	X	X	
ECG <sup>c</sup>	X	X	X			X				X	X	X	X		
Concomitant medications	X	X									X	X	X		
Urine drug screen <sup>d</sup>	X	X													
Urinalysis (including microalbumin) <sup>d</sup>	X	X				X							X	X	
Serum pregnancy test (screening only)	X														
Urine pregnancy test (dipstick)		X													
Follicle stimulating hormone	X														
Hepatitis and HIV	X														
TSH	X														

**Table 4.2-1 Schedule of Study Procedures (Cohorts 1-3)**

Study Period	Screening		Treatment Period										Follow-up				
	Day -28 (Day -56) to Day -2 <sup>a</sup>	Day -1	V1 Day 1 (Dose 1)		D2	V2	V3 Day 8 (Dose 2)		V4 Day 15 (Dose 3)		D16	V5	V6	V7	V8	V9	
Day/Visit			0 hr	EOI hr	12 hr			0 hr	EOI hr								
<b>Time point/Procedure</b>																	
HbA1c	X																
Serum chemistry <sup>e</sup>	X		X			X		X				X				X	
Hematology <sup>e</sup>	X		X			X		X						X		X	
Lipids for eligibility (fasting; TG, LDL-C [direct], HDL-C)	X																
Verify eligibility criteria	X	X															
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization			X														
Admit to inpatient unit		X					X										
<b>Investigational product administration</b>			X					X									
Assess systemic/local tolerability/infusion site reactions <sup>f</sup>			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK blood sample for mass and activity <sup>e</sup>			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK blood sample (Pacific Biomarkers)			X					X								X	
PD blood sample for key lipid, lipoprotein biomarkers, and apoA1 and apoB <sup>e</sup>			X		X	X	X	X	X	X	X	X	X	X	X	X	
PD blood sample for other apolipoprotein biomarkers (apoAII, apoCIII and apoE) <sup>e</sup>			X									X				X	

**Table 4.2-1 Schedule of Study Procedures (Cohorts 1-3)**

Study Period	Screening		Treatment Period						Follow-up				
	Day -28 (Day -56) to Day -2 <sup>a</sup>	Day -1	V1		V2	V3	V4		V5	V6	V7	V8	V9
			Day 1 (Dose 1)	Day 2			Day 15 (Dose 2)	Day 16					
Time point/Procedure			0 hr	EOI 12 hr		0 hr	EOI 12 hr						
PD blood sample for preβ1-HDL <sup>c</sup>			X	X				X	X				
ADA/nAb blood sample <sup>e*</sup>			X			X					X	X	X
													
													

apoA1 = apolipoprotein A1; apoB = apolipoprotein B; apoE = apolipoprotein E; ADA = anti-drug antibody; AE = adverse event; BP = blood pressure; CEC = cholesterol efflux capacity; D = Day; dECG = digital electrocardiogram; ECG = electrocardiogram; HbA1c = glycated hemoglobin; HDL = high density lipoprotein; EOI = end of infusion; HDL-C = high-density lipoprotein-cholesterol; HIV = human immunodeficiency virus; LCAT = lecithin-cholesterol acyltransferase; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein-cholesterol; nAb = neutralizing antibody; PD = pharmacodynamics; PK = pharmacokinetics; SAE = serious adverse event; SID = subject identification (number); TG = triglycerides; TSH = thyroid stimulating hormone; V = visit; VLDL = very low-density lipoprotein.

<sup>a</sup> Day -56 to Day -2 only for subjects who require a washout of an applicable concomitant medication.

<sup>b</sup> Vital signs (blood pressure, respiratory rate, heart rate, pulse oximetry, body temperature) on Day 1, 8, and 15 should be collected pre-dose (within 60 minutes prior to start of dosing); every 15 minutes (± 2 minutes) during the infusion; 0.5, 2 hours (± 15 minutes), and 6 hours (± 30 minutes) after completion of infusion. Day 2 collection should be 24 hours (± 60 minutes) post dose. Day 5: 96 ± 3 hours post dose, Day 16: 24 hours (± 60 minutes) post dose, Day 19: 96 ± 3 hours post dose, Day 22: 168 ± 24 hours post dose, Day 29 ± 1 day (Days 28-30) post dose, Day 43±2 days (Days 41-45) post dose, Day 71±4 days post dose.

<sup>c</sup> Digital ECG will be obtained prior to blood sampling and after 10 minutes of supine (or semi-recumbent) rest. All ECGs should be captured in triplicate (three unique ECGs), with all three ECGs being captured within a 5 minute window. Each dECG will also be printed and should be stored in the subject's source file. On Days 1, 8, and 15 predose triplicate ECGs should be collected at 3 different times within 60 minutes prior to dosing with each set being separated by at least 5 minutes (3 × 3 replicates) and 0.5 and 6 hours (± 30 minutes) post-dose. Day 2: 24 hours (± 60 minutes) post dose, Day 5: 96 ± 3 hours post dose, Day 16: 24 hours (± 60 minutes) post dose, Day 19: 96 ± 3 hours post dose, Day 22: 168 ± 24 hours post dose, Day 29± 1 day (Days 28 -30), Day 43±2 days (Days 41-45).

<sup>d</sup> Day -1 to be performed locally, all other scheduled testing (including screening) to be performed centrally.

- e Time frames for laboratory testing, if designated for testing (by an X) in the table: Day 1: predose (within 60 minutes prior to dosing); end of infusion (within 5 minutes after completion of infusion); and 12 hours ( $\pm 30$  minutes) post dose, Day 2: 24 hours ( $\pm 60$  minutes) post dose, Day 5: 96  $\pm$  3 hours post dose, Day 8: predose (within 60 minutes prior to dosing); and end of infusion (within 5 minutes after completion of infusion), Day 15: predose (within 60 minutes prior to dosing); end of infusion (within 5 minutes after completion of infusion); and 12 hours ( $\pm 30$  minutes) post dose, Day 16: 24 hours ( $\pm 60$  minutes) post dose, Day 19: 96  $\pm$  3 hours post dose, Day 22: 168  $\pm$  24 hours post dose, Day 29  $\pm$  1 day (Day 28-30), Day 43  $\pm$  2 days (Day 41-45), Day 71  $\pm$  4 days (Day 67-75). \*ADA will be tested on Days 1 and 15 predose (within 60 minutes prior to dosing) and on Days 29, 43 and 71 within the time-windows specified above.
- f Days 1, 8, and 15 to be assessed predose (within 60 minutes prior to dosing) and 5, 30, 60 minutes ( $\pm 5$  minutes), 4 hours ( $\pm 30$  minutes), 6 hours and 12 hours ( $\pm 30$  minutes) post dose. Day 2 and Day 16: 24 hours ( $\pm 60$  minutes) post dose. Day 5: 96  $\pm$  3 hours post dose, Day 19: 96  $\pm$  3 hours post dose, Day 22: 168  $\pm$  24 hours post dose, Day 29  $\pm$  1 day (Day 28-30), Day 43  $\pm$  2 days (Day 41-45)
- g Future use blood samples will be stored for potential future analysis [REDACTED] Blood volumes and aliquots would need to be adjusted accordingly.

**Table 4.2-2 Schedule of Study Procedures (Cohort 4)**

Study Period	Screening		Treatment Period										Follow-up				
	Day -28 (Day -56 to Day -2 <sup>a</sup> )	Day -1	V1			V2			V3	V4			V5	V6	V7	V8	V9
			Day 1 (Dose 1)	D2	Day 3 (Dose 2)	D5	Day 10 (Dose 3)	D11	D14	D17	D24	D38	D66				
Time point/Procedure	0 hr	EOI	12 hr	0 hr	EOI	6 hr	0 hr	EOI	12 hr	0 hr	EOI	12 hr					
Main study informed consent / assignment of SID number	X																
Future use informed consent (optional)	X																
Medical history (including cardiovascular history)	X																
Body weight	X																X
Height	X																
Physical examination	X						X							X		X	X
Vital signs (BP, respiratory rate, pulse, pulse oximetry, body temperature) <sup>b</sup>	X						X				X			X		X	X
ECG <sup>c</sup>	X						X				X			X		X	
Concomitant medications	X						X							X		X	X
Urine drug screen <sup>d</sup>	X																
Urinalysis (including microalbumin) <sup>d</sup>	X						X							X		X	X
Serum pregnancy test (screening only)	X																
Urine pregnancy test (dipstick)		X															
Follicle stimulating hormone	X																



**Table 4.2-2 Schedule of Study Procedures (Cohort 4)**

Study Period	Screening		Treatment Period						Follow-up					
	Day -28 (Day -56) to Day -2 <sup>a</sup>	Day -1	V1 Day 1 (Dose 1)		V2 Day 3 (Dose 2)		V3 D5	V4 Day 10 (Dose 3)		V5 D14	V6 D17	V7 D24	V8 D38	V9 D66
Time point/Procedure	0 hr	EOI 12 hr	0 hr	EOI 6 hr	0 hr	EOI 12 hr		0 hr	EOI 12 hr					
ApoA1 and ApoB <sup>b</sup>							X							
PD blood sample for other apolipoprotein biomarkers (apoAII, apoCIII and apoE) <sup>c</sup>	X									X	X			
PD blood sample for preβ1-HDL <sup>c</sup>	X	X				X	X	X		X	X			
ADA/nAb blood sample <sup>e*</sup>	X						X				X	X	X	X

apoA1 = apolipoprotein A1; apoB = apolipoprotein B; apoE = apolipoprotein E; ADA = anti-drug antibody; AE = adverse event; BP = blood pressure; CEC = cholesterol efflux capacity; D = Day; dECG = digital electrocardiogram; ECG = electrocardiogram; EOI = end of infusion; HbA1c = glycated hemoglobin; HDL = high density lipoprotein; HDL-C = high-density lipoprotein-cholesterol; HIV = human immunodeficiency virus; LCAT = lecithin-cholesterol acyltransferase; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein-cholesterol; nAb = neutralizing antibody; PD = pharmacodynamics; PK = pharmacokinetics; SAE = serious adverse event; SID = subject identification (number); TG = triglycerides; TSH = thyroid stimulating hormone; V = visit; VLIDL = very low-density lipoprotein.

<sup>a</sup> Day -56 to Day -2 only for subjects who require a washout of an applicable concomitant medication.

<sup>b</sup> Vital signs (blood pressure, respiratory rate, heart rate, pulse oximetry, body temperature) on Days 1, 3, and 10 should be collected pre-dose (within 60 minutes prior to start of dosing); 0.5 (± 2 minutes), 2 hours (± 15 minutes), and 6 hours (± 30 minutes) post dose. Days 2 and 11 collection should be 24 hours (± 60 minutes) after completion of infusion post dose, Day 5 should be 48 hours ± 2 hours post dose, Day 14: 96 ± 3 hours post dose, Day 17: 168 ± 24 hours post dose, Day 24 ± 1 day (Days 23-25) post dose, Day 38 ± 2 days (Days 36-40) post dose, Day 66 ± 4 days post dose (Day 62-70).

<sup>c</sup> Digital ECG will be obtained prior to blood sampling and after 10 minutes of supine (or semi-recumbent) rest. All ECGs should be captured in triplicate (three unique ECGs), with all three ECGs being captured within a 5 minute window. Each dECG will also be printed and should be stored in the subject's

source file. On Days 1, 3, and 10 predose triplicate ECGs should be collected at 3 different times within 60 minutes prior to dosing with each set being separated by at least 5 minutes (3 × 3 replicates) and 0.5 and 6 hours (± 30 minutes) post-dose. Days 2, and 11: 24 hours (± 60 minutes) post dose, Day 5 should be 48 hours ± 2 hours post dose, Day 14: 96 ± 3 hours post dose, Day 17: 168 ± 24 hours post dose, Day 24 ± 1 day (Days 23 -25), Day 38 ± 2 days (Days 36-40).

- <sup>d</sup> Day -1 to be performed locally, all other scheduled testing (including screening) to be performed centrally.
- <sup>e</sup> Time frames for laboratory testing, **if designated for testing (by an X)** in the table: Days 1 and 10: predose (within 60 minutes prior to dosing); and 12 hours (± 30 minutes) post dose, Day 2: 24 hours (± 60 minutes) post dose, Day 3: predose (within 60 minutes prior to dosing). Day 5 should be 48 hours ± 2 hours post dose, Day 11: 24 hours (± 60 minutes) post dose, Day 14: 96 ± 3 hours post dose, Day 17: 168 ± 24 hours post dose, Day 24 ± 1 day (Day 23-25), Day 38 ± 2 days (Day 36-40), Day 66 ± 4 days (Day 62-70). \* **ADA will be tested on Days 1 and 10 predose (within 60 minutes prior to dosing) and on Days 24, 38 and 66 within the time-windows specified above.**
- <sup>f</sup> Days 1 and 10 to be assessed predose (within 60 minutes prior to dosing) and 5, 30, 60 minutes (± 5 minutes), 4 hours (± 30 minutes), 6 hours and 12 hours (± 30 minutes) post dose. Days 2: 24 hours (± 60 minutes) post dose. Day 3: predose (within 60 minutes prior to dosing) and 5, 30, 60 minutes (± 5 minutes), 4 hours (± 30 minutes) and 6 hours (± 30 minutes) post dose. Day 5: 48 hours ± 2 hours post dose, Day 11: 24 hours (± 60 minutes) post dose. Day 14: 96 ± 3 hours post dose, Day 17: 168 ± 24 hours post dose, Day 24 ± 1 day (Day 23-25), Day 38 ± 2 days (Day 36-40).
- <sup>g</sup> Time frames for laboratory testing, if designated for testing (by an X) in the table: Day 1: predose (within 60 minutes prior to dosing); end of infusion (within 5 min post dose) (PK only); 30 and 90 minutes (± 5 minutes), 4 hours and 12 hours (± 30 minutes) post dose, Day 2: 24 hours (± 60 minutes) post dose, Day 3: predose (within 60 minutes prior to dosing); end of infusion (within 5 min post dose) (PK only) and 6 hours post dose (± 30 minutes). Day 5: 48 hours (± 2 hours) post dose. Day 10: predose (within 60 minutes prior to dosing); end of infusion (within 5 min post dose) (PK only); and 12 hours (± 30 minutes) post dose, Day 11: 24 hours (± 60 minutes) post dose, Day 14: 96 ± 3 hours post dose, Day 17: 168 ± 24 hours post dose, Day 24 ± 1 day (Day 23-25), Day 38 ± 2 days (Day 36-40), Day 66 ± 4 days (Day 62-70).
- <sup>h</sup> Day 1: predose (within 60 minutes prior to dosing); 30, and 90 minutes (± 5 minutes), 4 hours and 12 hours (± 30 minutes) post dose, Day 10: predose (within 60 minutes prior to dosing). Day 14: 96 ± 3 hours post dose, Day 17: 168 ± 24 hours post dose, Day 24 ± 1 day (Day 23-25), Day 38 ± 2 days (Day 36-40),
- <sup>i</sup> Future use blood samples will be collected on Day 1 predose (within 60 minutes prior to dosing), 90 minutes (± 5 minutes), and 4 hours (± 30 minutes). Day 2: 24 hours post dose (± 60 minutes). Day 10: predose (within 60 minutes prior to dosing). Day 11: 24 hours post dose (± 60 minutes). Day 17: 168 ± 24 hours post dose, Day 24 ± 1 day (Day 23-25), Day 38 ± 2 days (Day 36-40), and Day 66 ± 4 days (Day 62-70). Future use blood samples will be stored for potential future analysis.

Blood volumes and aliquots would need to be adjusted accordingly.

**Table 4.2-3 Schedule of Study Procedures for Additional Follow-up for Subjects with ADA-positive Results (All Cohorts)**

Study Period	Additional Follow-up <sup>a</sup>				
Visit Number	V10	V11	V12	V13	V14
Procedure / Study Week	Week 14 Day 100 (± 4 days)	Week 18 (±2 weeks)	Week 31 (±2 weeks)	Week 44 (±2 weeks)	Week 57 (±2 weeks)
Targeted physical examination	X	X	X	X	X
Vital signs	X	X	X	X	X
Serum chemistry and hematology	X	X	X	X	X
Urinalysis (including microalbumin)	X	X	X	X	X
PK blood sample (mass and activity)	X	X	X	X	X
PK blood sample (Pacific Biomarkers) <sup>b</sup>	X	X	X	X	X
PD blood sample for key lipid and lipoprotein biomarkers and apoA1, fasting <sup>c</sup>	X	X	X	X	X
ADA/nAb blood sample	X	X	X	X	X
Assessment of AEs/SAEs	X	X	X	X	X
Concomitant medications	X	X	X	X	X

ADA = anti-drug antibody; apoA1 = apolipoprotein AI; AE = adverse event; CE = cholesteryl ester; FC = free cholesterol; HDL-C = high-density lipoprotein-cholesterol; HDL-CE = high-density lipoprotein cholesteryl ester; HDL-UC = high density lipoprotein-unesterified cholesterol; LDL-C = low-density lipoprotein-cholesterol; nAb = neutralizing antibody; PD = pharmacodynamics; PK = pharmacokinetics; SAE = serious adverse event; TC = total cholesterol; TG = triglycerides; V = visit; VLDL-C = very low-density lipoprotein-cholesterol.

<sup>a</sup> Subjects whose Day 71 (Cohorts 1-3) Day 66 (Cohort 4) immunogenicity sample is confirmed as ADA positive will return to the study site on Weeks 14 and 18 and approximately every 3 months thereafter for additional assessments until their immunogenicity sample is no longer ADA positive or until approximately 12 months after the Day 43 visit, whichever occurs first. The study site will be notified if a subject needs to come back or not for additional visits. Subjects whose immunogenicity sample is no longer ADA positive will not have to return to the study site.

<sup>b</sup> Samples will be stored and analyzed as needed

<sup>c</sup> HDL-C, TC, FC, CE, HDL-CE, HDL-UC, non-HDL-C, non-HDL-CE, non-HDL-UC, LDL-C (direct measure), VLDL-C, TG and apoA1.

#### 4.2.1 Unscheduled Visits and Early Termination Visits

Depending on the purpose of the visit and discussion with the medical monitor (if necessary), the following procedures may be performed at unscheduled visits and for subjects who terminate prematurely from the study:

- Targeted physical examination
- Vital signs
- ECG

- Serum chemistry and hematology
- Urinalysis (including microalbumin)
- PK blood sample (mass and activity)
- PD blood sample for key lipid and lipoprotein biomarkers (HDL-C, TC, FC, CE, HDL-CE, HDL-UC, non-HDL-C, non-HDL-CE, non-HDL-UC, LDL-C [direct measure], VLDL-C, TG, apoB) and apoA1
  - For early termination visits, this sample should be taken with the subject fasted.
  - For unscheduled visits, this sample should be taken with the subject fasted only if possible.
- ADA/nAb blood sample
- Assessment of AEs/SAEs
- Concomitant medications

### **4.3 Description of Study Procedures**

#### **4.3.1 Medical History, Physical Examination, Electrocardiograms, Weight, and Vital Signs**

##### **4.3.1.1 Medical History and Physical Examination**

Medical history at screening will include history and current medical conditions, past or present CV disorders, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatologic, psychiatric, genitourinary, drug and surgical history, or any other diseases or disorders.

A full physical examination will be conducted at screening, Day -1, and the Day 43 visits. Targeted physical examinations (evaluation of selective body systems at the judgement of the physician or qualified designee based on subject presentation) will be conducted at the remaining time points. On dosing days, the physical examination is to be conducted predose (Table 4.2-1, Table 4.2-2, and Table 4.2-3).

Physical examinations will be performed by a physician or qualified designee with examination of the following body systems: immunologic/allergy; head, ears, eyes, nose, throat; respiratory; CV; gastrointestinal; musculoskeletal; focused neurologic; (to the extent of determining whether or not the subject is willing and able to cooperate with the required study procedures in the investigator's judgment); dermatologic; hematologic/lymphatic; and endocrine.

Any focal deficit identified at baseline should be documented in the electronic case report form (eCRF). Clinically significant abnormal findings will be recorded at baseline and follow-up.

Height and body weight will be measured at screening and weight repeated at the Day 71 (Cohorts 1-3) Day 66 (Cohort 4) visit.

#### **4.3.1.2 Systemic/Local Tolerability**

Site staff will check the infusion/injection site(s) for local reactions and assess for systemic reactions at the times specified in the study procedures tables. Local and systemic reactions will be recorded as AEs according to the criteria described in Section 5.1.

#### **4.3.1.3 Vital Signs**

Vital sign measurements (BP, respiratory rate, heart rate, pulse oximetry, and body temperature) will be measured on all days at time points specified in the Schedules of Procedures (Table 4.2-1, Table 4.2-2, and Table 4.2-3).

Vital signs are to be obtained after the subject has rested in the supine position for at least 5 minutes. For subjects who are not able to remain supine, a semi-recumbent position within 45 degrees of supine is allowed. For time points where ECG recording precedes vital sign measurement, the 10-minute rest in the supine (or semi-recumbent) position prior to the ECG suffices for the rest prior to vital sign measurement. Route of body temperature measurement will be according to local custom.

Subjects should refrain from smoking or drinking caffeinated beverages within 4 hours prior to vital signs measurements.

Subjects must remain in the same position, supine or semi-recumbent, for the entire measurement and should be consistent for the entire study. The use of automated devices for measuring BP and heart rate is acceptable, although when done manually, BP should be taken in the upper arm, and heart rate must be measured in the brachial/radial artery for at least 30 seconds.

All BP determinations must be performed using calibrated and appropriately maintained equipment and should be used on the same subject throughout the study as much as possible. The same size BP cuff, which has been properly sized and calibrated, should be used to measure BP each time.

Subject's arm must be at the same height (at the level of their heart) during each BP measurement.

At screening, BP should be measured on 2 consecutive occasions, once on each arm, to determine which arm potentially has the higher reading. Measurement from a single arm is

acceptable when only one arm is accessible. This same arm should be used, whenever possible, for each BP assessment.

Peripheral capillary oxygen saturation (SpO<sub>2</sub>) measurements from pulse oximetry should be recorded after confirmation of an adequate SpO<sub>2</sub> waveform.

For pulse oximetry determination, nail polish and/or pressed nails should be removed or an alternate site utilized.

#### **4.3.1.4 Electrocardiograms**

Electrocardiography will be used in this study to monitor cardiac safety. ECGs will be conducted at time points as presented in the Schedules of Procedures (Table 4.2-1 and Table 4.2-2). ECGs will be recorded after the subject has rested for at least 10 minutes in the supine position. For subjects who are not able to remain supine, semi-recumbent position within 45 degrees of supine is allowed. Subjects must remain in the same position, supine or semi-recumbent, for the entire measurement and should be consistent for the entire study.

The following variables will be reported: RR, PR, QRS, and QT intervals. Derived parameters (such as heart rate, QTcF and others as applicable) will be calculated.

ECG and vital sign measures immediately precede PK and PD sample times. Whenever possible, it is preferable to have meals consumed after ECGs or to perform ECGs  $\geq$  1.5 hours after a meal, to avoid the influence of food intake on heart rate, T-wave morphology, and QT assessment.

#### **12-lead Electrocardiograms**

ECGs will be recorded digitally and printed on paper. ECGs at each time point will be captured in triplicate (ie, 3 separate 12-lead ECGs at least 1-2 minutes apart within a 5-minute window) at the designated time points. The printed paper ECGs will be used for “real time” bedside ECG assessment by the investigator (or designee) who will be responsible for the overall interpretation and determination of the clinical significance of any potential ECG findings. Digital ECGs will be submitted to the ECG core lab, which will perform the digital ECG analysis and interpretation in this study using standard methodology. If the central reader identifies an abnormality, per the study alert criteria, the investigator will be notified and will review the ECG and report any AEs as necessary.

The investigator may record 12-lead ECGs at other time points if there are any abnormal findings or if the investigator considers it is required for any other safety reason.

Digital ECGs will be submitted to the sponsor (or designee) and to the ECG vendor. The ECG vendor will perform the analysis and interpretation in this study using their digital ECG methodology. If the central reader finds an abnormality that the clinician may have missed, the ECG vendor will notify the investigator and the sponsor, and the investigator will review the ECG and report any AEs as necessary.

On each day of investigational product administration, three sets of predose triplicate digital ECGs will be collected. Each triplicate set must be separated by at least 5 minutes, and performed within 60 minutes prior to dosing.

#### **4.3.2 Clinical Laboratory Tests**

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study.

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed central or licensed local clinical laboratory. Serum pregnancy test will be conducted at screening only. Urine pregnancy test will be conducted on Day -1. Urine pregnancy tests may be performed at the site using a licensed test (dipstick). Clinically significant (as determined by the investigator) abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

The following clinical laboratory tests will be performed:

##### **Serum Chemistry**

- Calcium
- Chloride
- Potassium
- Sodium
- Bicarbonate
- Aspartate transaminase (AST)
- Alanine transaminase (ALT)
- Alkaline phosphatase (ALP)
- Total bilirubin
- Gamma glutamyl transferase
- Creatinine
- Blood urea nitrogen
- Glucose
- Albumin
- Creatine kinase (CK)

**Note for serum chemistries:** Tests for AST, ALT, ALP, and total bilirubin must be conducted concurrently and assessed concurrently.

##### **Hematology**

- White blood cell count with differential (% and absolutes)
- Platelet count

- Red blood cell count
- Hematocrit
- Hemoglobin
- Mean corpuscular volume
- Mean corpuscular hemoglobin concentration

### Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Microalbumin
- Blood
- Leukocyte esterase
- Bilirubin
- Urobilinogen
- Nitrite
- Urine microscopy and urine casts (as required)
- Urine drug screen (screening only)

Note: Breath alcohol testing is acceptable as an alternative to urine testing

### Pregnancy Test (females only)

- Serum  $\beta$ -hCG (beta human chorionic gonadotropin) (at screening only)
- Urine hCG

### Lipids for Eligibility (screening only, fasting for a minimum of 6 hours)

- Triglycerides
- LDL-C (by direct measure)
- HDL-C

### Other Safety Tests (screening only)

- Thyroid stimulating hormone (at screening only) , including T4 as applicable
- HbA1c (at screening only)
- Follicle-stimulating hormone (females only)
- Hepatitis B surface antigen, hepatitis C antibody
- HIV-1, -2 antibodies

### 4.3.3 Pharmacokinetic Evaluation and Methods

The PK sampling (mass and activity) times and windows for collection are specified in the Schedules of Procedures in [Table 4.2-1](#), [Table 4.2-2](#), and [Table 4.2-3](#). Sampling within the specified window around the specified time will not be considered a protocol deviation but the exact time of sampling should be recorded. The concentration of MEDI6012 will be determined by immunoassay.

#### 4.3.4 Pharmacodynamic Evaluation and Methods

Blood samples for key lipid and lipoprotein biomarkers, pre $\beta$ 1-HDL, and apolipoprotein biomarkers will be collected at time points as presented in the Schedules of Procedures (Table 4.2-1, Table 4.2-2, and Table 4.2-3).

The PD markers of primary interest are HDL-C, HDL-CE, and CE; however, additional lipids and lipoproteins will also be collected and analyzed to fully describe the effect of MEDI6012 on the cholesterol pathway including but not limited to other measures in the lipid profile (TC, FC, HDL-UC, non-HDL-C, non-HDL-CE, non-HDL-UC, LDL-C [direct measure], VLDL-C, TG, apoB, apoA1, and, at some time points, apoAII, apoCIII, apoE). Pre $\beta$ 1-HDL will be characterized by enzyme-linked immunosorbent assay (ELISA).

##### PD blood sample for key lipid, lipoprotein biomarkers, ApoA1 and ApoB

- Total Cholesterol
- Free Cholesterol
- Esterified Cholesterol
- HDL-C
- HDL-CE
- HDL-UC
- Non-HDL-C
- Non-HDL-CE
- Non-HDL-UC
- VLDL-C
- Triglycerides
- LDL-C (direct)
- Calculated LDL-C
- ApoAI
- ApoB

##### PD blood sample for other apolipoprotein biomarkers

- ApoE
- ApoAII
- ApoCIII

In addition, for research purposes, [REDACTED]

#### 4.3.5 Immunogenicity Evaluation and Methods

As with any biologic agent, administration of MEDI6012 may induce the formation of ADA. Because MEDI6012 is the recombinant human form of endogenous LCAT, there is a theoretical risk of developing a nAb response against endogenous LCAT.

Blood samples for ADA will be collected at time points specified in the Schedules of Procedures (Table 4.2-1, Table 4.2-2, and Table 4.2-3). A screening assay will be used to

determine ADA-positive samples. This will be in the form of a traditional ligand-binding “bridging” assay using electrochemiluminescence. Any positive samples will be tested in a confirmatory assay whereby the specificity of the ADA response will be confirmed as either positive or negative with respect to MEDI6012 investigational product. Titer evaluation will be performed on samples that are confirmed positive for ADA, and these samples will be further characterized as either a neutralizing or a non-neutralizing antibody response using an enzymatic assay that determines the ability of LCAT to esterify a fluorescent analogue of cholesterol.

Immunogenicity data will be evaluated on an ongoing basis over the course of the study. ADA data up to Day 43 will be required for each DEC meeting. If a subject has a positive ADA result at Day 43, an additional 28 days will be required for the follow-up of ADA and HDL-C. If in the event that for  $\geq 1$  MEDI6012 subject the HDL-C AUC after Dose 3 is reduced by  $\geq 30\%$  relative to the response after Dose 1, ADA/nAb data through Day 43 and Day 71 (Cohorts 1-3) or Day 38 and Day 66 (Cohort 4) (if required) will be reviewed as part of the dose-escalation decision for that cohort (Section 3.1.3). If in the event that for  $\geq 1$  MEDI6012 subject the HDL-C is reduced  $\geq 30\%$  relative to the predose level at any time point during the study or ADA titer  $\geq 8$  that is on the rise, ADA/nAb data through Day 71 (Cohorts 1-3) or Day 66 (Cohort 4) will be reviewed as part of the dose-escalation decision for that cohort (Section 3.1.3).

In addition, subjects whose Day 71 (Cohorts 1-3) or Day 66 (Cohort 4) immunogenicity sample is confirmed as ADA positive will return to the study site on Weeks 14 and 18 and approximately every 3 months thereafter for additional assessments until their immunogenicity sample is no longer ADA positive or until 12 months after the Day 43 (Cohorts 1-3) or Day 38 (Cohort 4) visit, whichever occurs first. After each subsequent visit, the study site will be notified if a subject needs to come back or not for additional visits. Subjects whose immunogenicity sample is no longer ADA positive will not have to return to the study site. If a MedImmune safety review board determines that an adverse safety signal is attributed to the ADA-positive signal, then follow-up may continue beyond 12 months for subjects whose immunogenicity sample continues to be ADA positive. In addition, if it is deemed necessary to follow a subject more frequently than every 3 months, this may be recommended as an unscheduled visit.

#### **4.3.6 Estimate of Blood Volume to Be Collected**

The maximum volume of blood to be collected from each subject from screening through end of the Day 71 (Cohorts 1-3) Day 66 (Cohort 4) study visit is estimated to be 356 mL (Cohorts 1-3) or 440 mL (Cohort 4). Subjects who consent to collection of future use samples

will have an estimated additional [REDACTED] mL of blood drawn throughout the study for a total blood volume collection estimation of [REDACTED] mL (Cohorts 1-3) or [REDACTED] mL (Cohort 4). Additional blood samples may be collected at the discretion of the investigator in the event of abnormal laboratory findings or an AE. Furthermore, subjects with a positive ADA will return on Weeks 14 and 18 and then every 3 months and have blood drawn for a volume up to 35 mL per visit for up to 5 additional visits, as applicable.

#### 4.4 Study Suspension or Termination

The sponsor reserves the right to temporarily suspend or terminate this study at any time. The reasons for temporarily suspending or terminating the study may include but are not limited to the following:

1. Day 43 (Cohorts 1-3), Day 38 (Cohort 4), or Day 71 (Cohorts 1-3), Day 66 (Cohort 4) HDL-C point estimate for  $\geq 1$  MEDI6012 subject is reduced by  $\geq 30\%$  relative to the baseline point estimate (excluding other causes for HDL reduction, ie, acute infection) for that subject (indicating a meaningful decrease in endogenous LCAT activity relative to prestudy baseline levels) **and** is accompanied by:
  - A clinically significant safety finding, and/or
  - A positive result for nAb

If this criterion is met, no additional subjects will be dosed and subjects who have received investigational product will continue to be followed for safety, PK/PD, and immunogenicity. A MedImmune safety review board will review the totality of data and determine whether to continue or terminate the study.

Other reasons for temporarily suspending or terminating the study may include but are not limited to the following:

1. Anaphylaxis in any subject assessed as related to MEDI6012
2.  $\geq 1$  subject meeting Hy's Law
3. The incidence or severity of AEs indicates a potential health hazard to subjects
4. Subject enrollment is unsatisfactory
5. Non-compliance that might significantly jeopardize the validity or integrity of the study
6. Sponsor decision to terminate investigational product development

If MedImmune determines that temporary suspension or termination of the study is required, MedImmune will discuss the reasons for taking such action with all participating investigators (or head of the medical institution, where applicable). When feasible,

MedImmune will provide advance notice to all participating investigators (or head of the medical institution, where applicable) of the impending action.

If the study is suspended or terminated for safety reasons, MedImmune will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. MedImmune will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the Institutional Review Board (IRB) promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs when applicable) will be obtained prior to resuming the study.

## 4.5 Investigational Products

### 4.5.1 Identity of Investigational Product

MedImmune will provide the investigator(s) with investigational product and IV bag protectant (IVBP) using designated distribution centers ([Table 4.5.1-1](#)).

**Table 4.5.1-1 Identification of Investigational Products**

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
MEDI6012	MedImmune	Lyophilized powder (100 mg per mL upon reconstitution with sWFI) in a buffer consisting of 10 mM sodium phosphate, 300 mM sucrose, 0.06% (w/v) poloxamer-188 at pH 7.2.
Placebo	MedImmune	10 mL of a solution containing 10 mM sodium phosphate, 300 mM sucrose, 0.06% (w/v) poloxamer-188 at pH 7.2.
IVBP	MedImmune	10 mL of a solution containing 10 mM sodium phosphate, 300 mM sucrose, 0.06% (w/v) poloxamer-188 at pH 7.2.

IVBP = intravenous bag protectant; sWFI = sterile water for injection; w/v = weight by volume.

MEDI6012 is provided as a sterile white to off-white lyophilized powder (50 mg/vial, nominal). Upon reconstitution with 0.6 mL sterile water for injection (sWFI), MEDI6012 is a colorless to yellow solution.

Placebo is provided as a sterile colorless to slightly yellow solution

In addition to the investigational product, an IVBP solution is supplied to prevent adsorption of MEDI6012 to the IV infusion system. The IVBP is stored at 2°C to 8°C (36°C to 46°F).

The IVBP is supplied in 10R vials as a colorless to slightly yellow, clear to slightly opalescent liquid. Lyophilized MEDI6012 must not be reconstituted with the IVBP solution.

### **Investigational Product Kits**

Investigational product will be supplied to the site in containers in coded kits. The investigational product supplies will consist of 1-vial kits, and each kit will be labeled with a unique number (eg, 15854). This number will be identical to the number on the vial contained inside. The IVBP will consist of 10 vials per kit. Each IVBP kit will be labeled with a unique number (eg, 614001).

Every investigational product vial assigned by the IXRS is to be used for dose preparation. For the IV infusions, multiple vials of investigational product may be required for a single IV dose. Every investigational product vial assigned by the IXRS for dose preparation plus 1 vial of IVBP are to be used for every IV dose preparation and infusion. Each kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each container within the carton). Each carton is labeled with a unique number range that corresponds to the labeled number series of the containers within the carton.

#### **4.5.1.1 Investigational Product Dose Handling**

Since MEDI6012 and placebo are provided in unblinded kits, an unblinded pharmacist is required. Once prepared for administration, MEDI6012 and placebo remain potentially distinguishable, thus blinding will be maintained through use of tubing and IV bag covers for IV infusion and syringe covers for IV push injection.

MEDI6012, placebo and IVBP must be stored at 2°C to 8°C (36°F to 46°F) at all times unless they are being used for dose preparation.

MEDI6012 drug product requires reconstitution prior to use.

- Equilibrate vial(s) to room temperature for a minimum of 15 minutes. The reconstitution should be performed with 0.6 mL sWFI for each vial, with the liquid added gently to the side of the vial so the liquid stream is not directly added to the lyophilized cake. Commercially available sWFI will be supplied by the sites.
- Let the vial sit for 60 seconds before swirling. The vial should be gently rotated or swirled for 60 seconds and then let sit for an additional 60 seconds.
- Repeat this procedure until all the solids are dissolved. The vial should not be shaken or vigorously agitated. The reconstituted product should appear as a colorless to yellow and clear to opalescent solution. A thin layer of bubbles on the liquid surface is considered normal.

### **IV Infusion (Cohorts 1-3)**

Each IV infused dose will be delivered as an admixture of reconstituted MEDI6012 and IVBP or placebo plus IVBP, in a 0.9% (w/v) saline IV bag. The IVBP will be used for IV doses only. For each dose, inspect the lyophilized drug product vials, liquid placebo vials, liquid IVBP vials and 0.9% (weight by volume [w/v]) saline IV bag prior to preparation of active drug product dose or placebo dose. For active drug product arms, reconstitute only the required number of vials per dose of MEDI6012.

No incompatibilities between MEDI6012 and plastics (polyolefin without di-2-ethylhexyl phthalate [DEHP] bags and polypropylene syringes) have been observed when used in conjunction with the IVBP. Polyethylene/polyvinylchloride [PE/PVC] and PVC DEHP-free IV administration lines are acceptable. Lines should contain either 0.22 or 0.2 µm in-line polyethersulfone (PES) filter.

MEDI6012, placebo, and IVBP do not contain preservatives and any unused portion must be discarded. The total in-use storage time from needle puncture of the first investigational product vial(s) to start of IV administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If storage time exceeds these limits, a new dose must be prepared from a new investigational product vial(s), placebo and IVBP vial. If a prepared dose is stored at 2°C to 8°C (36°F to 46°F), equilibrate to room temperature and inspect prior to IV administration to ensure that the solution is clear.

### **IV Push (Cohort 4)**

Each IV push dose will be delivered as reconstituted MEDI6012 or placebo with a syringe and an IV administration set. IVBP should not be used for preparation of doses for Cohort 4. No incompatibilities have been observed with MEDI6012 in syringes (polycarbonate/polypropylene) and IV administration lines (PE/PVC and PVC DEHP-free). IV administration lines must contain either 0.22 or 0.2 µm in-line PES filter. Lines containing cellulose-based filters should not be used with MEDI6012, as these have not been tested. Dose 1 will be administered as 3 separate injections. Each injection will be administered over 30 seconds and each injection will be followed by a 10 mL normal saline flush. Dose 2 will be administered as 2 separate injections. Each injection will be administered over 30 seconds and each injection will be followed by a 10 mL normal saline flush. Dose 3 will be administered as a single injection over 30 seconds and followed by a 10 mL normal saline flush.

MEDI6012 and placebo do not contain preservatives and any unused portion must be discarded. The total in-use storage time from needle puncture of the first investigational product vial(s) to start of IV push administration should not exceed 4 hours at room temperature. If storage time exceeds these limits, a new dose must be prepared from a new vial(s).

#### **4.5.1.2 Investigational Product Inspection**

Each vial selected for dose preparation should be inspected. If there are any defects noted with the investigational product, the investigator and site monitor should be notified immediately. Refer to the Product Complaint section, Section 4.5.1.6, for further instructions.

#### **4.5.1.3 Dose Preparation Steps**

The dose of MEDI6012 or placebo for administration must be prepared by the unblinded investigational product manager or other qualified professional using aseptic technique. Only remove from storage the required MEDI6012 or placebo vials and IVBP vials required for subject dosing.

For the IV infused doses (Cohorts 1-3 only), IVBP must be used to precondition the IV bag prior to addition of the MEDI6012 or placebo dose (specific instructions below).

Follow the guidelines of the IV bag manufacturer for maximum number of allowable punctures through the injection port; if needed, use an intermittent adaptor for the dose preparation into the injection port.

#### **Preparation and Administration of MEDI6012 or Placebo for IV Infusion (Cohorts 1-3)**

The admixture for 40, 120, and 300 mg IV doses should be prepared in a 50 mL polyolefin 0.9% (w/v) saline IV bag containing IVBP using a single step dilution. The prepared dose will be delivered using a PVC (DEHP-free) IV administration set with a 0.22 or 0.2- $\mu$ m PES filter. Following completion of infusion, a flush of the IV administration set should be performed by adding up to 30 mL of 0.9% (w/v) saline (or equivalent corresponding to the hold-up volume of the extension set) to the IV bag to obtain the full dose. The dose preparation procedure is as follows in [Table 4.5.1.3-1](#).

**Table 4.5.1.3-1 Investigational Product Dose Preparation for 40 mg, 120 mg and 300 mg MEDI6012 or Placebo IV Doses**

Step	Instructions
Preparation of 40 mg dose of MEDI6012 or placebo for IV administration	<ol style="list-style-type: none"> <li>1. Obtain a 50 mL IV saline bag.</li> <li>2. Remove entire volume (ie, 50 mL saline plus the manufacturer’s overfill) from the IV bag. Do not discard.</li> <li>3. Add 50 mL of saline back into IV bag.</li> <li>4. Remove and discard a total volume of 2.4 mL saline from the IV bag.</li> <li>5. Slowly add 2.0 mL of IVBP. Mix the contents of the IV bag by gentle inversion for 30 seconds.</li> <li>6. Slowly add 0.4 mL of MEDI6012 from a reconstituted vial or placebo using a 3.0 mL syringe. Mix the contents of the IV bag by gentle inversion for 30 seconds.</li> <li>7. Inspect the IV bag to ensure solution is clear.</li> </ol>
Preparation of 120 mg dose of MEDI6012 or placebo for IV administration	<ol style="list-style-type: none"> <li>1. Obtain a 50 mL IV saline bag.</li> <li>2. Remove entire volume (ie, 50 mL saline plus the manufacturer’s overfill) from the IV bag. Do not discard.</li> <li>3. Add 50 mL of saline back into IV bag.</li> <li>4. Remove and discard a total volume of 3.2 mL saline from the IV bag.</li> <li>5. Slowly add 2.0 mL of IVBP. Mix the contents of the IV bag by gentle inversion for 30 seconds.</li> <li>6. Slowly add 1.2 mL of MEDI6012 from a reconstituted vial or placebo using a 3.0 mL syringe. Mix the contents of the IV bag by gentle inversion for 30 seconds.</li> <li>7. Inspect the IV bag to ensure solution is clear.</li> </ol>
Preparation of 300 mg dose of MEDI6012 or placebo for IV administration	<ol style="list-style-type: none"> <li>1. Obtain a 50 mL IV saline bag.</li> <li>2. Remove entire volume (ie, 50 mL saline plus the manufacturer’s overfill) from the IV bag. Do not discard.</li> <li>3. Add 50 mL of saline back into IV bag.</li> <li>4. Remove and discard a total volume of 5.0 mL saline from the IV bag.</li> <li>5. Slowly add 2.0 mL of IVBP. Mix the contents of the IV bag by gentle inversion for 30 seconds.</li> <li>6. Slowly add 3.0 mL of MEDI6012 from a reconstituted vial or placebo using a 3.0 mL syringe. Mix the contents of the IV bag by gentle inversion for 30 seconds.</li> <li>7. Inspect the IV bag to ensure solution is clear.</li> </ol>

IV = intravenous; IVBP = intravenous bag protectant.

**Preparation and Administration of MEDI6012 or Placebo by IV Push (Cohort 4)**

For each dose level delivered by IV push, [Table 4.5.1.3-2](#) describes the delivery volume (mL), the required number of vials, and number of required syringes for each dose.

**Table 4.5.1.3-2 Investigational Product IV Push Delivery Volume and Vial Usage**

Dose (mg)	Total Delivery Volume (mL)		Number of Vials Required		Number of 1 mL Syringes Required	
	MEDI6012	Placebo	MEDI6012	Placebo	MEDI6012	Placebo
300 (Dose #1)	3.0	3.0	6	1	3	3
150 (Dose #2)	1.5	1.5	3	1	2	2
100 (Dose #3)	1.0	1.0	2	1	1	1

IV = intravenous

MEDI6012 or placebo is pooled in each 1 mL syringe (polycarbonate/ polypropylene) and dosed based on the delivery volume as shown in Table 4.5.1.3-2. Each injection will be administered over 30 seconds and each injection will be followed by a 10 mL normal saline flush.

NOTE: The IVBP is not used in the preparation of IV push doses.

**4.5.1.4 Treatment Administration**

The first day of investigational product dosing is considered Day 1. On each day of dosing, following an overnight fast for a minimum of 6 hours, investigational product will be administered as soon as is practicable after rising.

Investigational product will be administered via IV infusion over a period of approximately 60 minutes ( $\pm$  5 minutes) (Cohorts 1-3) or IV push over approximately 1-3 minutes, inclusive of flush (Cohort 4).

**4.5.1.5 Monitoring of Dose Administration**

Vital signs and ECG assessments will be performed before and after dose administration according to the schedule of procedures.

As with any exogenous protein, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

**4.5.1.6 Reporting Product Complaints**

Any defects with the investigational product must be reported *immediately* to the MedImmune Product Complaint Department by the site with further notification to the site monitor. All defects will be communicated to MedImmune and investigated further with the

Product Complaint Department. During the investigation of the product complaint, all investigational products must be stored at labeled conditions unless otherwise instructed.

MedImmune contact information for reporting product complaints:

Email: [productcomplaints@medimmune.com](mailto:productcomplaints@medimmune.com)

Phone: +1-301-398-2105  
+1-877-MEDI-411 (+1-877-633-4411)

Fax: +1-301-398-8800

Mail: MedImmune, LLC  
Attn: Product Complaint Department  
One MedImmune Way  
Gaithersburg, MD USA 20878

#### **4.5.2 Additional Study Medications**

Subjects should continue to take their statin therapy at their regular prescribed dose, and any other medication(s) prescribed for their atherosclerotic CVD. MedImmune will not provide statin or any of these other medications.

#### **4.5.3 Labeling**

Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The label will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local languages, as required.

#### **4.5.4 Storage**

Investigational product and IV bag protectant are stored at 2°C to 8°C.

#### **4.5.5 Treatment Compliance**

Investigational product is administered by study site personnel, who will monitor compliance.

#### **4.5.6 Accountability**

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the

study, copies of investigational product accountability records will be returned to MedImmune. At the end of the study or upon request, all unused investigational product will be destroyed at the site as per the site's procedure and local regulation. Investigational product destruction capabilities will be evaluated during study feasibility, and if a site doesn't have the capabilities of destroying the investigational product on site, MedImmune will coordinate the return of the investigational product to a designated depot.

The investigational product manager will provide a copy of the site's written destruction procedure to the unblinded site monitor for review by MedImmune.

## **4.6 Treatment Assignment and Blinding**

### **4.6.1 Methods for Assigning Treatment Groups**

An IXRS will be used for randomization to a treatment group and assignment of blinded investigational product kit numbers. A subject is considered randomized into the study when the investigator notifies the IXRS that the subject meets eligibility criteria and the IXRS provides the assignment of blinded investigational product kit numbers to the subject.

For each cohort, 8 subjects will be randomized in a 6:2 ratio to receive MEDI6012 or placebo. Investigational product must be administered within 24 hours after randomization. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the medical monitor must be notified immediately.

### **4.6.2 Methods for Ensuring Blinding**

This is a blinded study in which the subjects and investigator and contract research organization personnel are blinded to investigational product, and MedImmune staff involved in the study are unblinded. MEDI6012 and placebo are not identical in appearance. Neither the subject nor any of the investigator staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (International Council for Harmonisation [ICH E9]). Since MEDI6012 and placebo are not identical in packaging, investigational product will be handled by an unblinded investigational product manager at the site and will be masked prior to administration through the use of tubing or IV bag covers (Cohorts 1-3) and syringe covers (Cohort 4). An independent investigational product monitor will also be unblinded to perform investigational product accountability. In the event that the treatment allocation for a subject becomes known to the investigator or other study staff involved in the management of study subjects, the sponsor must be notified *immediately*. If the treatment allocation for a subject needs to be known to treat an individual subject for an

AE, the investigator must notify the sponsor *immediately*. The site will maintain a written plan detailing which staff members are blinded/unblinded and the process of investigational product administration used to maintain the blind.

### **4.6.3 Methods for Unblinding**

#### **4.6.3.1 Unblinding in the Event of a Medical Emergency**

In the event of a medical emergency, the investigator may unblind an individual subject's investigational product allocation. Instructions for unblinding an individual subject's investigational product allocation are contained in the IXRS manual. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received investigational product. In the majority of cases, the management of a medical emergency would be the same whether or not investigational product was received by the subject. If this was the case, the investigational product allocation should not be unblinded.

MedImmune retains the right to unblind the treatment allocation for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

### **4.7 Restrictions During the Study and Concomitant Treatment(s)**

Subjects must refrain from strenuous exercise for approximately 48 hours prior to each study day where blood samples for safety (hematology and serum chemistry) will be collected, from screening through final study assessment.

The investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF.

#### **4.7.1 Permitted Concomitant Medications**

It is anticipated that subjects enrolled to this study and with established atherosclerotic CVD will be managed per current treatment guidelines (eg, AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and Other Atherosclerotic Vascular Disease, 2011 and ACC/AHA Blood Cholesterol Guideline, 2013) and may therefore be receiving a range of cardio-protective medications, with the exception of prohibited lipid-lowering therapies. Subjects should adhere to their current regimen from screening through end of the study.

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as “excluded” as listed in Section 4.7.2. Specifically, subjects should continue to take their regular prescribed dose of statin and blood pressure medication and receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

#### **4.7.2 Prohibited Concomitant Medications**

Concomitant medications, including over-the-counter medications, herbal supplements, and vitamins that may affect control of lipids (except for statins) are prohibited from screening through the final study visit (see Exclusion Criterion 10 for explanation of washout period and [Appendix 5](#) for a list of therapies requiring wash-out). Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

Due to their effect on lipids, systemic corticosteroids within 28 days prior to screening and throughout the study are also prohibited, except if needed to treat a generalized allergic reaction, anaphylaxis as defined in [Appendix 3](#), or other serious medical condition. Inhaled, intranasal, topical, ophthalmic, and intra-articular corticosteroids are permitted. Systemic corticosteroid use should first be discussed with and permitted by the medical monitor.

### **4.8 Statistical Evaluation**

#### **4.8.1 General Considerations**

Data will be provided in listings sorted by cohort, treatment group, and subject number. Tabular summaries will be presented by treatment group with placebo group combined when appropriate. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, minimum, and maximum. Baseline values will be defined as the last valid assessment prior to the first administration of investigational product. Details of endpoint analyses will be described in the statistical analysis plan (SAP).

#### **Definition of Analysis Population**

The As-treated Population includes all subjects who receive at least one dose of study investigational product. Subjects will be analyzed according to the treatment they actually receive.

The PK Population includes all subjects in the As-treated Population who have at least one detectable LCAT serum concentration measurement.

#### 4.8.2 Sample Size and Power Calculations

[Redacted]

[Redacted]

#### 4.8.3 Safety

##### 4.8.3.1 Analysis of Adverse Events

Safety analysis will be based on the As-treated Population. AE collection begins after the subject signs the informed consent document and lasts until the end of the study. TEAEs and TESAEs will be coded by the most updated version of the Medical Dictionary for Regulatory Activities (MedDRA), and the type, incidence, severity, and relationship to investigational product will be summarized. Specific AEs will be counted once for each subject for calculating percentages. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of relationship observed will be reported. All TEAEs and TESAEs will be summarized overall, as well as categorized by MedDRA system organ class and preferred term.

##### 4.8.3.2 Analysis of Clinical Laboratory Parameters

Clinical laboratory safety tests including serum chemistry, hematology, and others will be summarized using descriptive statistics at each time point by treatment group with placebo group combined. Change from baseline to each post baseline time point in these data will also be summarized, where appropriate.

#### **4.8.3.3 Analysis of Vital Signs**

Vital sign results will be summarized using descriptive statistics at each time point by treatment group.

#### **4.8.3.4 Analysis of ECGs**

ECG parameters will also be assessed and summarized descriptively by treatment group.

As part of the cardiac safety evaluation for MEDI6012, a prospectively defined exposure-response analysis for MEDI6012 concentrations and change from baseline ECG intervals will be performed, using data from this study and the previous single ascending dose study, to thoroughly characterize the QTcF and other ECG intervals. A pre-specified workflow will be described in a separate technical document. Results from the exposure-response analysis will not be reported in the CSR.

#### **4.8.4 Immunogenicity**

ADA incidence rate and titer will be tabulated for each treatment group. Samples confirmed positive for ADA will be tested and analyzed for nAb and summarized similarly.

#### **4.8.5 Pharmacokinetics**

Non-compartmental analysis will be performed for MEDI6012 treated subjects. Serum MEDI6012 mass and activity concentration-time profiles will be summarized by dose cohort. The PK parameters to be reported include  $C_{max}$ , time of maximal concentration ( $T_{max}$ ), AUC, accumulation ratio, and  $t_{1/2}$ . Descriptive statistics for PK parameters will be provided.

Additional PK analyses may be conducted as appropriate. If the data allow, population PK analysis will be performed but will not be reported in the CSR.

#### **4.8.6 Pharmacodynamics**

The PD parameters of primary interest are the baseline-adjusted HDL-C, HDL-CE, and CE  $AUC_{0-96hr}$  following Dose 3 administration ( $AUC_{0-96hr \text{ Dose } 3}$ ). AUC will be calculated using the trapezoidal rule. Statistical comparison between treatment groups with placebo group combined will be conducted using analysis of covariance (ANCOVA) by adjusting baseline HDL-C and treatment group. The dose-response profile with regard to HDL-C may be explored using MCP-MOD procedure. Other endpoints including  $AUC_{0-96hr \text{ Dose } 1}$ ,  $AUC_{0-168h \text{ Dose } 1}$ ,  $AUC_{0-168h \text{ Dose } 3}$ , and  $AUC_{1-22d}$  (AUC from time 0 on Day 1 through 168 hours after Dose 3) for HDL-C, TC, FC, CE, HDL-CE, HDL-UC, non-HDL-C, non-HDL-CE,

non-HDL-UC, LDL-C (by direct measure), apoA1 and apoB will be analyzed similarly to the primary PD endpoint.

Change and the percent change from baseline at each time point for each of the above lipids, lipoproteins, and apolipoproteins as well as VLDL-C, TG, pre $\beta$ 1-HDL, apoAI, apoAII, apoCIII, and apoE will be analyzed and compared using ANCOVA by adjusting baseline and treatment group with placebo group combined.

For ANCOVA, if the data is not normally distributed, the analyses will be conducted on rank-transformed data.

Descriptive statistics will be provided by treatment group for  $R_{\max}$  (maximum biomarker response) and  $(R)T_{\max}$  (time to reach maximum biomarker response) for each of these as well. Details of these analyses will be specified in the SAP.

#### 4.8.7 Exploratory Endpoints



#### 4.8.8 Timing of Analyses

A primary analysis of the safety, immunogenicity, PK, and PD data will be conducted after the last subject has completed or dropped out prior to the last scheduled visit (Day 71 (Cohorts 1-3) Day 66 (Cohort 4) and will be reported in the CSR. The long-term follow-up data will be reported as an addendum to the CSR.

## 5 ASSESSMENT OF SAFETY

### 5.1 Definition of Adverse Events

The ICH Guideline for Good Clinical Practice E6(R1) defines an AE as:

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires

medical intervention by the investigator, or a finding judged by the investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cells increased). Abnormal laboratory values that are not, in the investigator's opinion, medically significant and do not require intervention should not be reported as AEs.

AEs may be treatment emergent (ie, occurring after initial receipt of investigational product) or non-treatment emergent. A non-treatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or non-serious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or serious adverse event (SAE).

## **5.2 Definition of Serious Adverse Events**

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

## **5.3 Definition of Adverse Events of Special Interest**

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid

communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

Hepatic function abnormality meeting the definition of Hy's law is considered an AESI. See Section 5.6.2 for the definition and reporting of AESIs of hepatic function abnormality.

## 5.4 Recording of Adverse Events

AEs will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. AEs will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to the sponsor (see Section 5.5). See Section 5.2 for the definition of SAEs and [Appendix 2](#) for guidelines for assessment of severity and relationship.

If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form.

Infusion of biological products is commonly associated with infusion related reactions. Anaphylaxis and infusion-related reactions have some common manifestations and may be difficult to distinguish from each other. Infusion-related reactions are commonly observed during or shortly after the first time of exposure to biological products delivered through IV infusion. These reactions are less common following subsequent exposures. Unlike infusion-related reactions, anaphylaxis is a rare event, usually occurring after subsequent exposure to an antigen, and it is most commonly accompanied by severe systemic, skin and/or mucosal reactions. The investigator is advised to carefully examine symptoms of adverse reactions observed during or shortly after exposure to MEDI6012, and consider the above mentioned facts prior to making a final diagnosis. Reactions occurring at the time of or shortly after subsequent infusions of investigational product are to be judged by the investigator at his/her own discretion. For the investigator's convenience and in order to facilitate consistency in judgments a copy of the National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) guidance for anaphylaxis diagnosis is provided in [Appendix 3](#).

### 5.4.1 Time Period for Collection of Adverse Events

Adverse events will be collected from time of signature of informed consent throughout the treatment period until end of Day 71 (Cohorts 1-3) or Day 66 (Cohort 4). For ADA/nAb positive, SAE collection will be continued until end of the follow-up period(s). After Day 71

(Cohorts 1-3) or Day 66 (Cohort 4), only those AEs determined by the investigator as related to investigational product will be collected.

#### **5.4.2 Follow-up of Unresolved Adverse Events**

Any AEs that are unresolved at the subject's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

### **5.5 Reporting of Serious Adverse Events**

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform the appropriate sponsor representative(s) within 1 day, ie, immediately, but no later than 24 hours of becoming aware of the event.

The designated sponsor representative works with the investigator to ensure that all the necessary information is provided to the sponsor patient safety data entry site within 1 calendar day of initial receipt for fatal and life threatening events and within 5 calendar days of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform sponsor representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but no later than 24 hours after becoming aware of the event.

Once the investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to inform the designated sponsor representative(s).

If the EDC system is not available, then the investigator or other study site personnel reports an SAE to the appropriate sponsor representative by telephone. The sponsor representative will advise the investigator/study site personnel how to proceed.

## 5.6 Other Events Requiring Immediate Reporting

### 5.6.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of the maximum dose specified by the clinical study protocol.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose with a MedImmune investigational product occurs during the course of the study, then the investigator or other site personnel inform appropriate sponsor representatives immediately, or no later than 24 hours after becoming aware of the event.

The designated sponsor representative works with the investigator to ensure that all relevant information is provided to the sponsor's patient safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply; see Section 5.5. For other overdoses, reporting must occur within 30 days.

### 5.6.2 Hepatic Function Abnormality

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT  $\geq 3 \times$  ULN together with total bilirubin  $\geq 2 \times$  ULN may need to be reported as SAEs. Refer to [Appendix 4](#) for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

### 5.6.3 Pregnancy

Women of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur in a female subject, investigational product should be discontinued immediately and the pregnancy reported to the sponsor.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs during the study, then the investigator or other site personnel will inform the appropriate sponsor representatives within 1 day, ie, immediately but **no later than 24 hours** after becoming aware of the event.

The designated sponsor representative works with the investigator to ensure that all relevant information is provided to the sponsor's patient safety data entry site within 1 or 5 calendar days for SAEs (see Section 5.5) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The pregnancy reporting module in the CRF is used to report the pregnancy and the pregnancy outcome module is used to report the outcome of the pregnancy.

#### **5.6.3.1 Paternal Exposure**

Male subjects should refrain from fathering a child or donating sperm during the study and for 6 weeks following the last dose of investigational product.

Pregnancy of the subject's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality), occurring from the date of the first dose until 6 weeks after the last dose should, if possible, be followed up and documented.

## **6 STUDY AND DATA MANAGEMENT**

### **6.1 Training of Study Site Personnel**

Before the first subject is entered into the study, a MedImmune representative will review and discuss the requirements of the clinical study protocol and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

## 6.2 Monitoring of the Study

During the study, a MedImmune representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The MedImmune representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct. Members of the TIMI Study Group may also be available for information and contact the sites as needed.

### 6.2.1 Source Data

Refer to the Clinical Study Agreement for location of source data.

### 6.2.2 Study Agreements

The Principal Investigator at each center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this clinical study protocol and the Clinical Study Agreement, the terms of clinical study protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between MedImmune and the Principal Investigator must be in place before any study-related procedures can take place, or subjects are enrolled.

### 6.2.3 Archiving of Study Documents

The investigator follows the principles outlined in the Clinical Study Agreement.

### **6.3 Study Timetable and End of Study**

An individual subject will be considered to have completed the study if the subject was followed through Day 71 (Cohorts 1-3) or Day 66 (Cohort 4), regardless of the number of doses of investigational product that was received.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up.

The end of the study (“study completion”) is defined as the date of the last protocol-specified visit/assessment for the last subject in the study (ie, the Day 71 (Cohorts 1-3) or Day 66 (Cohort 4) visit). If one or more subjects are determined to be ADA positive at this Day 71 (Cohorts 1-3) or Day 66 (Cohort 4) visit, then study completion will be defined as the date of the last visit/assessment for the last ADA-positive subject.

### **6.4 Data Management**

MedImmune Data Management will be accountable for the data management of this study according to the Data Management Plan.

A Web Based Data Capture system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

### **6.5 Medical Monitor Coverage**

Each subject will be provided with contact information for the Principal Investigator. In addition, each subject will receive a toll-free number intended to provide the subject’s physician access to a medical monitor 24 hours a day, 7 days a week in the event of an emergent situation where the subject’s health is deemed to be at risk. In this situation, when a subject presents to a medical facility where the treating physician or health care provider requires access to a physician who has knowledge of the investigational product and the clinical study protocol and the Principal Investigator is not available, the treating physician or health care provider can contact a medical monitor through this system, which is managed by a third party vendor.

## **7 ETHICAL AND REGULATORY REQUIREMENTS**

### **7.1 Ethical Conduct of the Study**

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

### **7.2 Subject Data Protection**

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

### **7.3 Ethics and Regulatory Review**

An IRB should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The investigator will ensure the distribution of these documents to the applicable IRB, and to the study site staff.

The opinion of the IRB should be given in writing. The investigator should submit the written approval to MedImmune before enrolment of any subject into the study.

The IRB should approve all advertising used to recruit subjects for the study.

MedImmune should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB annually.

Before enrolment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

MedImmune will handle the distribution of any of these documents to the national regulatory authorities.

MedImmune will provide Regulatory Authorities, IRB and Principal Investigators with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions (SUSARs), where relevant.

Each Principal Investigator is responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. MedImmune will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

#### **7.4 Informed Consent**

The Principal Investigator(s) at each center will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an IRB

#### **7.5 Changes to the Protocol and Informed Consent Form**

Study procedures will not be changed without the mutual agreement of the Coordinating Investigator and MedImmune.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol.

The amendment is to be approved by the relevant IRB and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

MedImmune will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to IRB see Section 7.3.

If a protocol amendment requires a change to a site's Informed Consent Form, MedImmune and the site's IRB are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each IRB.

## **7.6 Audits and Inspections**

Authorized representatives of MedImmune, a regulatory authority, or an IRB may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact MedImmune immediately if contacted by a regulatory agency about an inspection at the site.

## 8 REFERENCES

Amar MJ, Shamburek RD, Vaisman B, Knapper CL, Foger B, Hoyt RF, Jr. et al. Adenoviral expression of human lecithin-cholesterol acyltransferase in nonhuman primates leads to an antiatherogenic lipoprotein phenotype by increasing high-density lipoprotein and lowering low-density lipoprotein. *Metabolism*. 2009;58(4):568-75.

Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, Jr. et al. 2011 ACCF/AHA Focused Update Incorporated Into the ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;123(18):e426-579.

Asztalos BF, Roheim PS, Milani RL, Lefevre M, McNamara JR, Horvath KV et al. Distribution of ApoA-I-containing HDL subpopulations in patients with coronary heart disease. *Arterioscler Thromb Vasc Biol*. 2000;20(12):2670-6.

Brousseau ME, Kauffman RD, Herderick EE, Demosky SJ, Jr., Evans W, Marcovina S et al. LCAT modulates atherogenic plasma lipoproteins and the extent of atherosclerosis only in the presence of normal LDL receptors in transgenic rabbits. *Arterioscler Thromb Vasc Biol*. 2000;20(2):450-8.

Chen Z, Ichetovkin M, Kurtz M, Zycband E, Kawka D, Woods J et al. Cholesterol in human atherosclerotic plaque is a marker for underlying disease state and plaque vulnerability. *Lipids Health Dis*. 2010;9:61.

Czarnecka H, Yokoyama S. Regulation of cellular cholesterol efflux by lecithin:cholesterol acyltransferase reaction through nonspecific lipid exchange. *J Biol Chem*. 1996;271(4):2023-8.

Duivenvoorden R, Holleboom AG, van den Bogaard B, Nederveen AJ, de Groot E, Hutten BA et al. Carriers of lecithin cholesterol acyltransferase gene mutations have accelerated atherogenesis as assessed by carotid 3.0-T magnetic resonance imaging [corrected]. *J Am Coll Cardiol*. 2011;58(24):2481-7.

Fielding CJ, Fielding PE. Molecular physiology of reverse cholesterol transport. *J Lipid Res*. 1995;36(2):211-28.

Gille A, Easton R, D'Andrea D, Wright SD, Shear CL. CSL112 enhances biomarkers of reverse cholesterol transport after single and multiple infusions in healthy subjects. *Arterioscler Thromb Vasc Biol*. 2014;34(9):2106-14.

Glomset JA. The plasma lecithins:cholesterol acyltransferase reaction. *J Lipid Res*. 1968;9(2):155-67.

Gordts SC, Muthuramu I, Nefyodova E, Jacobs F, Van Craeyveld E, De Geest B. Beneficial effects of selective HDL-raising gene transfer on survival, cardiac remodelling and cardiac function after myocardial infarction in mice. *Gene Ther.* 2013;20(11):1053-61.

Haase CL, Tybjaerg-Hansen A, Qayyum AA, Schou J, Nordestgaard BG, Frikke-Schmidt R. LCAT, HDL cholesterol and ischemic cardiovascular disease: a Mendelian randomization study of HDL cholesterol in 54,500 individuals. *J Clin Endocrinol Metab.* 2012;97(2):E248-56.

Hoeg JM, Santamarina-Fojo S, Berard AM, Cornhill JF, Herderick EE, Feldman SH et al. Overexpression of lecithin:cholesterol acyltransferase in transgenic rabbits prevents diet-induced atherosclerosis. *Proc Natl Acad Sci U S A.* 1996;93(21):11448-53.

Kalakech H, Hibert P, Prunier-Mirebeau D, Tamareille S, Letournel F, Macchi L et al. RISK and SAFE signaling pathway involvement in apolipoprotein A-I-induced cardioprotection. *PLoS One.* 2014;9(9):e107950.

Kane JP, Malloy MJ. Prebeta-1 HDL and coronary heart disease. *Curr Opin Lipidol.* 2012;23(4):367-71.

Krause BR, Remaley AT. Reconstituted HDL for the acute treatment of acute coronary syndrome. *Curr Opin Lipidol.* 2013;24(6):480-6.

Kujiraoka T, Nanjee MN, Oka T, Ito M, Nagano M, Cooke CJ et al. Effects of intravenous apolipoprotein A-I/phosphatidylcholine discs on LCAT, PLTP, and CETP in plasma and peripheral lymph in humans. *Arterioscler Thromb Vasc Biol.* 2003;23(9):1653-9.

Kunnen S, Van Eck M. Lecithin:cholesterol acyltransferase: old friend or foe in atherosclerosis? *J Lipid Res.* 2012;53(9):1783-99.

Lamon-Fava S, Herrington DM, Reboussin DM, Sherman M, Horvath KV, Cupples LA et al. Plasma levels of HDL subpopulations and remnant lipoproteins predict the extent of angiographically-defined coronary artery disease in postmenopausal women. *Arterioscler Thromb Vasc Biol.* 2008;28(3):575-9.

Libby P, Aikawa M. Mechanisms of plaque stabilization with statins. *Am J Cardiol.* 2003;91(4A):4B-8B.

Marchesi M, Booth EA, Davis T, Bisgaier CL, Lucchesi BR. Apolipoprotein A-IMilano and 1-palmitoyl-2-oleoyl phosphatidylcholine complex (ETC-216) protects the in vivo rabbit heart from regional ischemia-reperfusion injury. *J Pharmacol Exp Ther.* 2004;311(3):1023-31.

Miida T, Nakamura Y, Inano K, Matsuto T, Yamaguchi T, Tsuda T et al. Pre beta 1-high-density lipoprotein increases in coronary artery disease. *Clin Chem*. 1996;42(12):1992-5.

Miller NE. Raising high density lipoprotein cholesterol. The biochemical pharmacology of reverse cholesterol transport. *Biochem Pharmacol*. 1990;40(3):403-10.

Nanjee MN, Cooke CJ, Garvin R, Semeria F, Lewis G, Olszewski WL et al. Intravenous apoA-I/lecithin discs increase pre-beta-HDL concentration in tissue fluid and stimulate reverse cholesterol transport in humans. *J Lipid Res*. 2001;42(10):1586-93.

Richart A, Heywood S, Reddy-luthmoodoo M, Natoli AK, Kiriazis H, Du X-J et al. Abstract 17001: Reconstituted High-density Lipoprotein (CSL-111) Infusion Improves Post-ischemic Heart Function Through Modulating the Acute Inflammatory Response and Angiogenesis. *Circulation*. 2015;132(Suppl 3):A17001-A.

Rosenson RS, Brewer HB, Jr., Davidson WS, Fayad ZA, Fuster V, Goldstein J et al. Cholesterol efflux and atheroprotection: advancing the concept of reverse cholesterol transport. *Circulation*. 2012;125(15):1905-19.

Rousset X, Vaisman B, Auerbach B, Krause BR, Homan R, Stonik J et al. Effect of recombinant human lecithin cholesterol acyltransferase infusion on lipoprotein metabolism in mice. *J Pharmacol Exp Ther*. 2010;335(1):140-8.

Rousset X, Shamburek R, Vaisman B, Amar M, Remaley AT. Lecithin cholesterol acyltransferase: an anti- or pro-atherogenic factor? *Curr Atheroscler Rep*. 2011;13(3):249-56.

Sethi AA, Sampson M, Warnick R, Muniz N, Vaisman B, Nordestgaard BG et al. High pre-beta1 HDL concentrations and low lecithin: cholesterol acyltransferase activities are strong positive risk markers for ischemic heart disease and independent of HDL-cholesterol. *Clin Chem*. 2010;56(7):1128-37.

Shah PK. High-density lipoprotein mimetics: focus on synthetic high-density lipoprotein. *The American journal of cardiology*. 2007;100(11):S62-S7.

Solajic-Bozicevic N, Stavljenic-Rukavina A, Sesto M. Lecithin-cholesterol acyltransferase activity in patients with coronary artery disease examined by coronary angiography. *Clin Investig*. 1994;72(12):951-6.

Tabas I, Williams KJ, Boren J. Subendothelial lipoprotein retention as the initiating process in atherosclerosis: update and therapeutic implications. *Circulation*. 2007;116(16):1832-44.

Tall AR. Cholesterol efflux pathways and other potential mechanisms involved in the athero-protective effect of high density lipoproteins. *J Intern Med*. 2008;263(3):256-73.

Tashiro J, Miyazaki O, Nakamura Y, Miyazaki A, Fukamachi I, Bujo H et al. Plasma pre beta1-HDL level is elevated in unstable angina pectoris. *Atherosclerosis*. 2009;204(2):595-600.

Theilmeyer G, Schmidt C, Herrmann J, Keul P, Schafers M, Herrgott I et al. High-density lipoproteins and their constituent, sphingosine-1-phosphate, directly protect the heart against ischemia/reperfusion injury in vivo via the S1P3 lysophospholipid receptor. *Circulation*. 2006;114(13):1403-9.

Williams KJ, Tabas I. The response-to-retention hypothesis of early atherogenesis. *Arterioscler Thromb Vasc Biol*. 1995;15(5):551-61.

Williams KJ, Feig JE, Fisher EA. Cellular and molecular mechanisms for rapid regression of atherosclerosis: from bench top to potentially achievable clinical goal. *Curr Opin Lipidol*. 2007;18(4):443-50.

Yvan-Charvet L, Welch C, Pagler TA, Ranalletta M, Lamkanfi M, Han S et al. Increased inflammatory gene expression in ABC transporter-deficient macrophages: free cholesterol accumulation, increased signaling via toll-like receptors, and neutrophil infiltration of atherosclerotic lesions. *Circulation*. 2008;118(18):1837-47.

Zhou M, Sawyer J, Kelley K, Fordstrom P, Chan J, Tonn G et al. Lecithin cholesterol acyltransferase promotes reverse cholesterol transport and attenuates atherosclerosis progression in New Zealand white rabbits. *Circulation*. 2009;120(18 Supplement):S1175.

## 9 CHANGES TO THE PROTOCOL

All changes described below have been incorporated into the current version of the protocol.

### 9.1 Protocol Amendment 1

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1. Key changes to the protocol are summarized in the table below.

**Table 9.1-1 Key Changes to the Protocol**

Key Details of Amendment	Reason for Amendment
Study Abstract: Updated	To be consistent with the changes made in the body of the protocol
Sections 1.6.1 (Primary Hypothesis), 1.6.2 (Secondary Hypothesis), 2.1.1, 2.1.2 (Primary and Secondary Objectives), and 2.2.1 (Primary Safety Endpoint) were updated to include Cohort 4 and one additional secondary hypothesis and objective	An additional cohort (Cohort 4) has been added to this study in order to provide data on this dose and dosing regimen to inform dose selection for future clinical studies.

**Table 9.1-1 Key Changes to the Protocol**

<b>Key Details of Amendment</b>	<b>Reason for Amendment</b>
Section 2.2.2 (Secondary Endpoints) was edited	Remove word duplication
Section 3.1.1 (Overview) Figure 3.1.1-1 (Study Flow Diagram and Additional Design Details) Section 3.1.2 and Table 3.1.2-1 (Treatment Regimen)	Updated to include relevant information for the addition of Cohort 4
Section 3.1.1 (Overview) Section 3.1.3 (Dose Escalation) list of biomarkers was clarified TEAE assessed by the “investigator” was changed to “sponsor” Cohort 4 was added as triggered from Cohort 2 DEC	To align with updated DEC charter  As the Sponsor has accountability for the safety of the subjects in the study To include the escalation to Cohort 4
Section 3.2.1 (Dose Rationale) was updated and Section 3.2.2 was added to include dose rationale and modeling for Cohort 4	Addition of the relevant information to provide the rationale for the doses to be included in Cohort 4
Section 4.1.1 (Number of Subjects) and 4.1.7 (Replacement of Subjects) were updated to include Cohort 4 Table 4.2-1 (Schedule of Study Procedures and footnotes) edited to correct typos and numbers: Numbers in footnotes were corrected “(Days 34-38)” to “(Days 41-45)” Table 4.2-1 (Schedule of Study Procedures and Footnotes) A clarifying sentence about ADA testing time points was added	Updated to include Cohort 4 subjects  Edited to correct typos and numbers  Edited for clarification
Section 4.1.3 (Exclusion Criteria) – previous exposure to rhLCAT was added as an additional exclusionary criterion	To avoid the risk of immunogenicity due to re-introduction of a previously washed out biologic
Table 4.2-2 (Schedule of Study Procedures Cohort 4) was added to protocol	To include Cohort 4 specific procedures
Table 4.2-2 is now Table 4.2-3 (due to the addition of an additional table of procedure for cohort 4) and title was updated to include “(all cohorts)” Reference to table numbers was corrected throughout	To accommodate Cohort 4  Due to change in table number
Section 4.2.1 (Unscheduled Visits and Early Termination Visits) was revised for clarification	Clarification to avoid unnecessary procedures on unscheduled visits
Section 4.3.1.2 (Systemic/Local Tolerability) was updated to include injection site reaction (in addition to infusion site reaction)	Due to the addition of Cohort 4 that will be administered via an IV push
Section 4.3.5 (Immunogenicity Evaluation and Methods) and Section 4.4 (Study Suspension or Termination) were updated to include Cohort 4 time points	Updated to include Cohort 4
Section 4.3.6 (Estimate of Blood Volume to Be Collected) was updated to include blood volumes specific to Cohort 4	Due to the addition of blood sampling time points specific to Cohort 4
Section 4.5.1.1 (Investigational Product Dose	Clarification and Cohorts 1-3 specific instructions

**Table 9.1-1 Key Changes to the Protocol**

Key Details of Amendment	Reason for Amendment
<p>Handling): subtitle “IV Administration” was changed to “IV Infusion (Cohorts 1-3)”, “extension was changed to administration” and filter information added</p> <p>Syringe covers were added for Cohort 4</p> <p>An additional section “IV Push (Cohort 4)” was added with specific instructions for Cohort 4</p>	<p>Adjusted text to clarify filter type</p> <p>To provide specific blinding information for Cohort 4</p> <p>To provide specific dose information instructions for Cohort 4</p>
<p>Section 4.5.1.3 Dose Preparation Steps – was split into two sub sections:</p> <p>“Preparation and Administration of MEDI6012 or Placebo for IV Infusion (Cohorts 1-3)’ and</p> <p>“Preparation and Administration of MEDI6012 or Placebo for Infusion by IV Push (Cohort 4)” with specific instructions for Cohort 4</p> <p>“w/v” was added for clarification</p>	<p>To provide specific instructions for Cohort 4</p> <p>Clarification</p>
<p>Table 4.5.1.3-2 Investigational Product IV Bolus Dose Delivery Volume and Vial Usage has been added</p>	<p>Cohort 4 specific instruction added</p>
<p>Sections 4.5.1.4 (Treatment Administration) and 4.6.2 (Methods for Ensuring Blinding) were updated to include Cohort 4</p>	
<p>Section 4.7.2 (Prohibited Concomitant Medications) and Appendix 5 Dietary Supplements, Prescription Drugs and Biologics Requiring or Not Requiring Wash-out – reference to Exclusion Criterion “15” was corrected to “10”</p>	<p>Number corrected</p>
<p>Section 4.8.2 (Sample Size and Power Calculations): total number of subjects was updated from 24 to 32 to include cohort 4</p>	<p>Number updated to include the subjects required for Cohort 4</p>
<p>Section 4.8.8 (Timing of Analysis), Section 5.4.1 (Time Period for Collection of Adverse Events), and Section 6.3 (Study Timetable and End of Study) were updated to include Cohort 4 time points</p>	<p>Updated to include Cohort 4</p>

## **Appendix 1      Signatures**

**SponsorSignature(s)**

**A Phase 2a Randomized, Blinded, Placebo-controlled Study to Evaluate the Safety,  
Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of MEDI6012  
in Subjects with Stable Atherosclerotic Cardiovascular Disease**

I agree to the terms of this protocol.

Signature and date: \_\_\_\_\_ Electronicsignatureattached

Boaz Hirshberg, MD

Clinical Therapeutic Area Head

One MedImmune Way, Gaithersburg MD, 20878, USA

Telephone number: +1 301-398-0645

**Signature of Principal Investigator**

**A Phase 2a Randomized, Blinded, Placebo-controlled Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Ascending Doses of MEDI6012 in Subjects with Stable Atherosclerotic Cardiovascular Disease**

I, the undersigned, have reviewed this protocol, and I agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I understand that the protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory authority and IRB/IEC, and must be approved by the IRB/IEC prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the sponsor, involves only logistical or administrative changes. Documentation of IRB/IEC approval must be sent to the sponsor immediately upon receipt.

Signature and date: \_\_\_\_\_

Name and title: \_\_\_\_\_

Address including postal code: \_\_\_\_\_  
\_\_\_\_\_

Telephone number: \_\_\_\_\_

Site/Center Number (if available) \_\_\_\_\_

This document contains confidential information, which should not be copied, referred to, released, or published without written approval from MedImmune or AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

## **Appendix 2      Additional Safety Guidance**

### **Assessment of Severity**

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. The determination of severity should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4 (life threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of death.
Grade 5 (fatal)	Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 5.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a non-serious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

### **Assessment of Relationship**

#### **Relationship to Investigational Product**

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product.

An event will be considered “not related” to use of the investigational product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the investigational product and the onset of the event (eg, the event occurred either before, or too long after, administration of the investigational product for it to be considered product-related)
- A causal relationship between the investigational product and the event is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the event is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related event)

Individual AE/SAE reports will be considered “related” to use of the investigational product if the “not related” criteria are not met.

“Related” implies that the event is considered to be “associated with the use of the drug” meaning that there is “a reasonable possibility” that the event may have been caused by the product under investigation (ie, there are facts, evidence, or arguments to suggest possible causation).

### **Relationship to Protocol Procedures**

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes nontreatment-emergent SAEs (ie, SAEs that occur prior to the administration of investigational product) as well as treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection, washout of an existing medication). The following guidelines should be used by investigators to assess the relationship of SAEs to the protocol:

Protocol related:       The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject’s medical record.

Not protocol related:   The event is related to an etiology other than the procedure/intervention that was described in the protocol (the alternative etiology must be documented in the study subject’s medical record).

### **Appendix 3 National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis**

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson FN Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report -- Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol.* 2006;117:391-7.

The National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)  
AND AT LEAST ONE OF THE FOLLOWING
  - a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
  - b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
  - c. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
  - d. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
  - e. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
  - f. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
  - a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
  - b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

## **Appendix 4      Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law**

### **Introduction**

This appendix describes the process to be followed to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets potential Hy's Law (PHL) criteria at any point during the study.

The investigator participates, together with MedImmune clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the investigational product.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting adverse events (AEs) and serious adverse events (SAEs) according to the outcome of the review and assessment in line with standard safety reporting processes.

### **Definitions**

#### **Potential Hy's Law**

Aspartate transaminase (AST) or alanine transaminase (ALT)  $\geq 3 \times$  upper limit of normal (ULN) **together with** total bilirubin (TBL)  $\geq 2 \times$  ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

#### **Hy's Law**

AST or ALT  $\geq 3 \times$  ULN **together with** TBL  $\geq 2 \times$  ULN, where no other reason, other than the investigational product, can be found to explain the combination of increases; eg, elevated ALP indicating cholestasis, viral hepatitis, or another drug.

For PHL and HL, the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

## Identification of Potential Hy's Law Cases

In order to identify cases of PHL, it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- $ALT \geq 3 \times ULN$
- $AST \geq 3 \times ULN$
- $TBL \geq 2 \times ULN$

When a subject meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (also sent to sponsor study representative).

The investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the investigator will:

- Notify the sponsor study representative
- Request a repeat of the test (new blood draw) by the central laboratory

When the identification criteria are met from central or local laboratory results the investigator will without delay:

- Determine whether the subject meets PHL criteria (see "Definitions" section) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

## Follow-up

### **PotentialHy'sLawCriteriaNotMet**

If the subject does not meet PHL criteria the investigator will:

- Inform the study representative that the subject has not met PHL criteria.
- Perform follow-up on subsequent laboratory results as deemed appropriate by the investigator.

### **Potential Hy's Law Criteria Met**

If the subject does meet PHL criteria the investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment
- Notify the sponsor study representative who will then inform the study team

The study physician contacts the investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up and the continuous review of data. Subsequent to this contact the investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the study physician.
- If at any time (in consultation with the medical monitor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

### **Review and Assessment of Potential Hy's Law Cases**

No later than 3 weeks after the biochemistry abnormality was initially detected, the medical monitor will contact the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the investigational product. The clinical medical monitor and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the sponsor's standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the investigational product:

- Report an SAE (report term ‘Hy’s Law’) according to the sponsor’s standard processes.
  - The ‘Medically Important’ serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of ‘related’ should be assigned

If, there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term ‘Potential Hy’s Law’) applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

## Appendix 5 Dietary Supplements, Prescription Drugs and Biologics Requiring or Not Requiring Wash-out

See Exclusion Criterion #10.

Prescription Drugs: Washout Required	Biologics Requiring Exclusion if Used Within Past 6 Months	Dietary Supplements: Washout Required	Dietary Supplements: No Washout Required
Gemfibrozil	evolocumab	≥ 2 grams/day of fish oil – Specifically refers to ≥ 2 grams/day DHA and EPA combined	Vitamin D
Fenofibrate	alirocumab	≥ 30 grams/day of flaxseed oil or ground flaxseed	Garlic
Bezafibrate	bococizumab	Red Yeast Extract – Banned by the FDA due to safety concerns	Foods containing stanols or healthy oils (eg, benecol, olivio, smart start, etc)
Ciprofibrate	ApoA1 Mimetics	Niacin OTC Supplement > 100 mg/day	Healthy oils (canola, olive oil)
Clinofibrate	RVX208		Nuts containing omega-3 fatty acids (eg, walnuts, almonds)
Clofibrate			Fish
Cholestyramine			Fiber-containing supplements (eg, Metamucil, oat bran, psyllium)
Colesevelam			Green tea extract
Colestipol			Policosanol (eg, bees wax, sugar cane)
Colesevelam hydrochloride			Guggulipid
Colestipol hydrochloride			Soybeans and soy protein
Niacin or Niaspan > 500 mg/day			Whey protein
Advicor (Subject should remain on lovastatin)			Vitamin E

ApoA1 = apolipoprotein A1; DHA = docosahexaenoic acid; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; OTC = over-the-counter.

<b>Document Name:</b>		d5780c00005-csp-amendment-1	
<b>Document Title:</b>	d5780c00005-csp-amendment-1		
<b>Document ID:</b>	Doc ID-003618619		
<b>Version Label:</b>	1.0 Approved CURRENT LATEST		
<b>Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)</b>	<b>SignedBy</b>	<b>Meaning of Signature</b>	
17-Jul-2017 13:34 GMT+0100		Clinical Operations Approval	
17-Jul-2017 15:02 GMT+0100		Nonclinical Scientist Approval	
18-Jul-2017 01:48 GMT+0100		Biostatistics Approval	
18-Jul-2017 15:37 GMT+0100		Medical Monitor Approval	
18-Jul-2017 23:04 GMT+0100		Clinical Approval	

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.